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IN THE

Supreme Court of the United States

PFIZER INC.,

Petitioner,

v.

APOTEX, INC. (formerly known as TorPharm, Inc.),

Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Prior to this Court's April 30, 2007 decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 127 S. Ct. 1727 (2007), the Court of Appeals for the Federal Circuit applied its then-existing version of the "teaching-suggestion-motivation" test for obviousness in this case and, despite district court findings that there would be no expectation of success in combining the two elements that resulted in the patented invention and that the combination was "unexpectedly superior" to the prior art, reversed the district court and found claims 1-3 of Pfizer's U.S. Patent No. 4,879,303 ("the '303 patent") to be obvious as a matter of law. This Court rendered its *KSR* decision while Pfizer's petition for rehearing was pending in the Federal Circuit, yet, despite both the substantial doubt that *KSR* cast upon that court's teaching-suggestion-motivation test and the fact that *KSR* reinforced the role that unexpected results can play in showing nonobviousness, the Federal Circuit failed to rehear or give any reconsideration to the case in light of that intervening development in the law. Three judges dissented from the denial of rehearing *en banc*.

The questions presented are:

1. Whether the Federal Circuit's failure to reconsider its judgment under the *KSR* standard merits summarily granting the petition, vacating the judgment, and remanding for further consideration in view of *KSR*?

2. Whether, if the petition is not granted prior to September 25, 2007—when Pfizer's pediatric exclusivity for Norvasc® comes to an end—the Court should instead grant the petition and order the Court of Appeals' judgment vacated under *United States v. Munsingwear, Inc.*, 340 U.S. 36 (1950), and *U.S. Bancorp Mortgage Co. v. Bonner Mall Partnership*, 513 U.S. 18 (1994).

PARTIES TO THE PROCEEDINGS AND CORPORATE DISCLOSURE STATEMENT

The parties before this Court are petitioner Pfizer Inc. and respondent Apotex, Inc. (formerly known as TorPharm, Inc.).

There is no parent company or publicly held company owning more than 10% of petitioner's stock.

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PETITION FOR A WRIT OF CERTIORARI

Pfizer Inc. respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The opinion of the United States District Court for the Northern District of Illinois was issued on January 17, 2006, and is unreported (App. 52a-68a).*

The panel opinion of the United States Court of Appeals for the Federal Circuit was issued on March 22, 2007, and is reported at 480 F.3d 1348 (App. 1a-38a). The Federal Circuit's order denying rehearing and rehearing *en banc*, over the dissents of three judges, is not yet reported; it can be found at 2007 U.S. App. LEXIS 11886 (App. 39a-51a).

JURISDICTION

The opinion of the United States Court of Appeals for the Federal Circuit was issued on March 22, 2007. App. 1a-38a. The Court of Appeals' order denying Pfizer's petition for rehearing *en banc* was issued on May 21, 2007. App. 39a-40a. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

Section 103(a) of Title 35, United States Code, provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

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* Two other district courts have also upheld claims 1-3 of the patent at issue here against obviousness challenges, based upon extensive findings of fact. *See Pfizer Inc. v. Mylan Labs., Inc.*, No. 02:02CV1628, 2007 WL 654274 (W.D. Pa. Feb. 27, 2007); *Pfizer Inc. v. Synthon Holdings BV*, No. 1:05CV39, 2006 WL 2553370 (M.D.N.C. Aug. 31, 2006).

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT

1. Pfizer is the assignee of U.S. Patent No. 4,879,303 ("the '303 patent") (Patent App. Tab 1), which covers amlodipine besylate. Amlodipine besylate is the active ingredient in Norvasc®, which is the world's largest selling brand-name drug for treating hypertension.

Pfizer scientists invented the compound amlodipine in 1981, and first sought to develop it as a cardiovascular drug in the form of amlodipine's maleate salt (amlodipine maleate). In an effort to create a commercially viable tablet form of amlodipine maleate, Pfizer scientists ran into two problems: One, amlodipine maleate was unstable, meaning that it produced numerous degradation products; two, it was too sticky, which meant that it adhered to tablet-making machinery and made mass production extraordinarily difficult. App. 3a-5a.

As the district court found, "[t]his was no small problem." App. 54a. Attempts to work around these problems by changing the excipients (the inactive substances used as the carrier of the drug) in the dosage form were unsuccessful. Two years into the project, with clinical trials well under way, the problems were so serious that the Pfizer scientist leading the project was seriously considering abandoning amlodipine entirely in favor of another candidate. Before abandoning the project entirely, however, the Pfizer scientists determined to try reacting amlodipine with other acids in order to create different salts of amlodipine. App. 54a. There was no basis to know if this would be successful, however, as the physicochemical properties of a new salt are entirely unpredictable. C.A. App. 884.

Pfizer scientists created a number of different salts and tested their properties. Amlodipine besylate, which was the reaction product of amlodipine and benzene sulphonic acid, resolved the instability and stickiness problems, but still maintained the good properties of amlodipine maleate (solubility and nonhygroscopicity—meaning a substance's tendency to attract and absorb moisture from the atmosphere). Amlodipine besylate was the only new salt that solved the problems of the prior art without introducing any new problems. App. 6a. As the district court found, "[t]his was no small task . . . many organic acids will not [produce an acceptable salt]. Some will only form oils, some are unstable, some produce undesirable or dangerous byproducts." App. 56a.

In October 1984, the inventors (Dr. Wells and Mr. Davison) made the extraordinary recommendation that Pfizer switch the salt form in its proposed drug product, after most of the safety and efficacy trials in humans had been completed. Pfizer accepted the recommendation, which was one that no pharmaceutical company would accept unless faced with serious formulation problems. C.A. App. 862, 938.

In April 1986, Pfizer applied for a U.K. patent on amlodipine besylate, and a counterpart U.S. application followed shortly thereafter. App. 6a. The application issued as the '303 patent on November 7, 1989. App. 8a.

2. Prior to Pfizer's application for a patent covering amlodipine besylate, there was only one other salt of amlodipine disclosed in the prior art—amlodipine maleate—which was disclosed in U.S. Patent No. 4,572,909 ("the '909 patent") (Patent App. Tab 2), also assigned to Pfizer. Importantly, nowhere in the '909 patent is there any reference to the besylate salt, to benzene sulphonic acid, nor for that matter any other member of the sulphonic acid group. The '909 patent identifies 12 acid anions as potential candidates for making salts, but each has a very different

structure than the besylate anion. App. 17a-18a; C.A. App. 884-85, 7672.

Apotex's obviousness theory was that, to an ordinarily skilled artisan, it would have been obvious to combine the '909 patent's amlodipine maleate with a January 1977 article (Berge, "Pharmaceutical Salts," *J. Pharm. Sci.* 66(1):1-19 (Jan. 1977)), whose Table 1 showed "53 FDA-approved, commercially marketed anions, including benzene sulphonate, that are useful for making pharmaceutically-acceptable salts, and lists the relative frequency of which each was used as a percentage based on the total number of anions or cations in use through 1974. Berge discloses that benzene sulphonate had a frequency of use of 0.25%." App. 8a.

Even so, one of ordinary skill in the art who looked beyond the '909 patent in April 1986 would have found an unlimited number of acids from which he or she might try to make a pharmaceutically acceptable salt of amlodipine by engaging a trial-and-error process. C.A. App. 884. Certainly, nothing pointed especially to the besylate anion: Besylate was a rarely used anion, present (as the Berge article showed) in only ¼ of 1 percent of drugs approved by the FDA as of 1977 (*i.e.*, one out of 400). By 1984, when amlodipine besylate was invented, there were only *two* drugs that had been approved by FDA in a besylate salt form: mesoridazine besylate and atracurium besylate. Neither was a cardiovascular drug, and neither belonged to the class of dihydropyridine compounds. Neither provided any information about the likelihood of even forming an amlodipine besylate salt, or what its properties might be. C.A. App. 887, 242-52.

As the district court here found: "As to whether the besylate salt is an actual improvement over the maleate, the Court recognizes that while not superior to the maleate salt in every category, the besylate salt clearly and unexpectedly illustrates a superior combination of properties when

compared to what was suggested as the preferred preparation, the maleate salt in the '909 patent. In addition to the evidence supplied by the exhibits in the patent, the Court notes the objective consideration that Pfizer would not have changed from the maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason." App. 65a-66a. Indeed, the Court concluded its opinion with this extraordinary praise for Pfizer's amlodipine besylate invention: "[T]he Court finds it to be an exceptional discovery, the besylate salt which finally produced a reliable delivery system." App. 67a.

3. On April 14, 2003, Apotex filed Abbreviated New Drug Application ("ANDA") No. 76-719 with the FDA, seeking to bring to market a generic version of Pfizer's Norvasc®. Apotex's ANDA represented that its proposed generic product was the same as Pfizer's Norvasc®, and that the '303 patent was not expired, but Apotex further averred that it was entitled to marketing approval because, in its view, the '303 patent was invalid and unenforceable. Under the Hatch-Waxman Act, the filing of this ANDA was itself an act of patent infringement. *See* 35 U.S.C. § 271(e)(2)(A). Accordingly, on July 30, 2003, Pfizer sued Apotex in order to defend its patent and defer any generic entry into the marketplace until after the pediatric exclusivity period for the '303 patent had expired, on September 25, 2007. App. 1a-2a; *see Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1275 (D.C. Cir. 2004) (explaining that 21 U.S.C. § 355a "authorizes an extra six-month pediatric exclusivity period following expiration of a drug patent for a patent holder that has satisfactorily conducted pediatric testing of its drug upon the FDA's request . . . .").

4. The District Court for the Northern District of Illinois held a bench trial from January 9 through January 17, 2006. On January 18, 2006, the district court issued its findings and conclusions, pursuant to FED. R. CIV. P. 52(a), from the bench, holding, *inter alia*, that claims 1-3 of the '303 patent

were nonobvious, and indeed represented "an exceptional discovery" and "an invention in its own right." App. 67a. Accordingly, the district court ordered that the FDA not approve Apotex's ANDA 76-719 prior to September 25, 2007. App. 67a-68a. That September 25, 2007 date was six months after the March 25, 2007 expiration of the '303 patent, representing the six additional months of pediatric exclusivity granted to Pfizer for amlodipine besylate pursuant to 21 U.S.C. § 355a(c)(2)(A)-(B).

5. On March 22, 2007, a panel of the Federal Circuit (with one judge concurring in the result only) reversed. Applying a version of its teaching-suggestion-motivation requirement, which has been criticized by this Court, the court held that "evidence of record easily satisfies us that a reasonable fact-finder could only conclude that Apotex has shown by clear and convincing evidence that the skilled artisan would indeed have been so motivated to combine the prior art to produce the besylate salt of amlodipine," and that, "contrary to the district court's finding, a reasonable fact-finder could only conclude that a skilled artisan would have had a reasonable expectation of success with the besylate salt of amlodipine." App. 19a.

6. Pfizer filed a petition for rehearing and rehearing *en banc*. While that petition was pending, this Court decided *KSR International Corp. v. Teleflex Inc.*, 550 U.S. ___, 127 S. Ct. 1727 (2007), which criticized the Federal Circuit's "rigid and mandatory" teaching-suggestion-motivation test and emphasized the important role of "unpredictability" in the nonobviousness analysis (*e.g.*, where elements combine in an "unexpected and fruitful manner," that will support a finding of nonobviousness). *Id.* at ___, 127 S. Ct. at 1740, 1741. Although Pfizer promptly filed a letter brief under FED. R. APP. P. 28(j), explaining why *KSR* supported rehearing, neither the panel nor the Federal Circuit *en banc* reconsidered the panel opinion to take *KSR* into account: the petition was denied on May 21, 2007, and the mandate was ordered to be issued immediately upon the denial. App. 40a.

Three judges dissented from the decision denying *en banc* rehearing. Judge Newman noted that "[b]oth sides acknowledge that the effects of chemical changes on properties of medicinal products is not predictable," and that the panel decision conflicted with the last sentence of 35 U.S.C. § 103(a), which commands that "[p]atentability shall not be negatived by the manner in which the invention was made." App. 41a. She also stressed that "[t]he ruling in this case has important policy as well as legal implications." App. 41a.

Judge Lourie dissented because "the panel failed to defer to fact-findings made by the district court that were not clearly erroneous regarding the unexpected properties of amlodipine besylate" (App. 47a), because "the panel improperly placed greater importance on the therapeutic value of a claimed compound over the value of its physical properties" (App. 47a), and because "the panel . . . found that the invention was the result of routine experimentation, and therefore was not patentable," which he (like Judge Newman) viewed as in conflict with the last sentence of 35 U.S.C. § 103(a). App. 48a. In addition, Judge Lourie noted that after *KSR*, a showing of unexpected properties (beyond biological properties) will take on a special importance in the pharmaceutical field, yet the panel opinion disdained such unexpected, non-biological properties entirely. Calling these issues ones of "exceptional importance," Judge Lourie voted to rehear the case, and dissented from the Federal Circuit's failure to do so. App. 49a.

Judge Rader also dissented. Like Judges Newman and Lourie, he chided the panel for discarding the undisputed testimony and evidence that "the properties of new pharmaceutical salt forms are entirely unpredictable" (App. 50a), noted that the panel's "obvious to try" approach was an ill fit in pharmaceutical cases (App. 50a-51a), and expressed concern that the panel's narrow focus on the fact that the besylate salt "showed no superior *therapeutic value*" was a myopic focus on just one of many properties of a

pharmaceutical product: "Although the maleate salt form was also therapeutically effective, the besylate form was still a significant improvement because it overcame the stability and processing problems that could have prevented successful commercial marketing." App. 51a (emphasis added).

Also like his dissenting colleagues, Judge Rader objected to the panel's disregard for the "patentability shall not be negatived by the manner in which the invention was made" requirement of 35 U.S.C. § 103(a); he explained why this had profound consequences for not just this case, but for all pharmaceutical patents: "Many if not most pharmaceutical inventions are discovered through a routine screening protocol or through an established trial and error process. Pharmaceutical inventions discovered by these routine screening methods include not only new formulations and salt forms, but also include the active pharmaceutical compounds themselves. Thus, this decision calls into question countless pharmaceutical patents, which in turn could have a profoundly negative effect on investments into the design and development of new life-saving pharmaceuticals." App. 51a.

REASONS FOR GRANTING THE WRIT

The importance of the issues in this case, as explained by the three dissenting judges in the Federal Circuit, would surely qualify this case for plenary review. But that is not a realistic possibility in this case, which will become moot no later than September 25, 2007, when Pfizer's pediatric-exclusivity period for amlodipine besylate comes to an end. So as a practical matter, the only chance of securing any relief from the erroneous judgment of the Court of Appeals in this case is to ask this Court to issue a GVR order — that is, to grant the petition, vacate the judgment below, and remand with instructions for the Federal Circuit to reconsider its decision in light of *KSR International Co. v. Teleflex, Inc.*, 550 U.S. ___, 127 S. Ct. 1727 (2007). The Federal Circuit

had every opportunity to do that, because *KSR* was handed down while Pfizer's rehearing petition was pending, but it failed to do so.

If this Court cannot review the case before September 25, 2007, then Pfizer alternatively requests the Court to vacate the judgment below and remand with instructions to dismiss under *United States v. Munsingwear, Inc.*, 340 U.S. 36 (1950), and *U.S. Bancorp Mortgage Co. v. Bonner Mall Partnership*, 513 U.S. 18 (1994). That outcome will avoid the inequities of having Pfizer saddled with the potential collateral-estoppel effect of a decision whose further review was prevented by the happenstance of patent expiry, and having future litigants (particularly in pharmaceutical cases) subject to an obviousness precedent of questionable correctness, and which took no account of this Court's *KSR* decision.

I. THIS CASE WARRANTS A GVR ORDER AS THE COURT OF APPEALS' DECISION IS PLAINLY IN TENSION WITH THIS COURT'S DECISION IN *KSR v. Teleflex*, WHICH THE FEDERAL CIRCUIT GAVE NO INDICATION OF CONSIDERING

This case is a textbook example of the type of case that warrants a GVR order, an order that this Court has described as an "integral part of this Court's practice, accepted and employed by all sitting and recent Justices." *Lawrence v. Chater*, 516 U.S. 163, 166 (1996). Such orders, which provide a vital mechanism for "conserv[ing] the scarce resources of this Court," are appropriate whenever each of three elements are met: (1) there have been "intervening developments, or recent developments that [the Court has] reason to believe the court below did not fully consider [that] reveal a reasonable probability that the decision below rests on a premise that the lower court would reject if given the opportunity for further consideration," (2) "it appears that such a redetermination may determine the ultimate outcome

of the litigation," and (3) the "equities of the case" favor a GVR order. *Id.*

All three are clearly present here. Shortly after the Federal Circuit issued its decision below invalidating the '303 patent on obviousness grounds, this Court's decision in *KSR* interpreted section 103(a) in a manner that cast substantial doubt on the Federal Circuit's then-prevailing teaching-suggestion-motivation requirement, demonstrating, at the very least, a "reasonable probability" that this "intervening development" might change the panel's obviousness analysis. And, as the Court of Appeals' obviousness determination was the sole basis on which it invalidated the patent, a different outcome on that question would almost certainly "determine the ultimate outcome of the litigation." Finally, on the equities, the profound consequences that the decision in this case will carry for pharmaceutical research and development in this country strongly suggest that the obviousness determination should be made with the benefit of an explicit consideration of this Court's latest guidance on the issue.

A. The Federal Circuit Invalidated The '303 Patent Based On a Version of Its Teaching-Suggestion-Motivation Test, Which Has Been Criticized By This Court.

Two issues here are beyond dispute—the Federal Circuit's obviousness analysis in this case was the *sole* basis on which it relied in denying Pfizer relief, and its obviousness analysis was predicated solely on pre-*KSR* obviousness precedents from that Court. Apotex conceded that its ANDA product (generic amlodipine besylate) would infringe the '303 patent. App. 35a-36a. And, while Apotex sought to defend against the infringement claim both on invalidity and unenforceability grounds, the only issue that the Federal Circuit reached was invalidity. App. 36a-37a. Moreover, the sole basis the court cited in declaring the patent invalid was its conclusion that the invention claimed in the '303

patent was obvious. In the panel's words: "From our *de novo* assessment of the determination below on obviousness . . . we conclude that the district court erred in holding that the claims of the '303 patent would not have been obvious." App. 37a.

In reaching that conclusion, the panel naturally relied on the then-current Federal Circuit obviousness standards. In particular, the court took its test from *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006), *pet. for cert. filed*, 75 U.S.L.W. 3484 (No. 06-1207, Mar. 5, 2007), under which "the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." App. 18a. And the court's treatment of the "motivation" element in that test clearly reflected that the court used that prong as a shorthand for the Circuit's teaching-suggestion-motivation test. Indeed, the decision expressly noted that the "suggestion, teaching or motivation to combine the relevant prior art teachings" does not "have to be found explicitly in the prior art references sought to be combined, but rather 'may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" App. 19a-20a (quoting *DyStar*, 464 F.3d at 1361). Applying *DyStar*'s implementation of the teaching-suggestion-motivation test, the court concluded that one skilled in the art "would have been motivated to combine the teachings [of the prior art] to produce the besylate salt of amlodipine." App. 23a.

The court then turned to consideration of the other factor from the *DyStar* test—whether one skilled in the art would have had a "reasonable expectation of success" in using besylate rather than maleate to combine with the amlodipine. At trial, Pfizer's expert witness had testified, without contradiction, that "one of ordinary skill in the art could

neither draw any conclusions nor have any expectations about the properties of amlodipine besylate from the properties of a besylate salt or a different compound." App. 42a (Newman, J., dissenting) (internal quotation marks omitted). Based on such testimony, the trial court had found as a matter of fact that "'the besylate salt clearly and unexpectedly exhibited a superior combination of properties when compared to what was suggested in the preferred preparation,'" and, accordingly, that it was not obvious. App. 47a (Lourie, J., dissenting) (quoting district court transcript).

The panel, however, rejected the obviousness determination, essentially holding, as one of the judges who dissented from the denial of rehearing noted, that whenever an "invention was the result of routine experimentation," it is "not patentable," notwithstanding that the results of that experimentation may have been surprising or unexpected. App. 48a (Lourie, J., dissenting). *See also* App. 31a (classifying Wells' efforts in discovering amlodipine besylate as "nothing more than routine application of a well-known problem-solving strategy" (internal quotation marks omitted)). To be sure, the court below attempted to limit that result to "the particularized facts of this case," App. 29a (emphasis omitted), but nowhere is any such limiting principle apparent in its opinion. As a consequence, numerous inventions in the pharmaceutical industry will be put at risk, as that industry is one in which new, surprising, and important advances often result from similar "routine experimentation," or trial-and-error efforts.

B. *KSR* Substantially Altered The Federal Circuit's Obviousness Framework

The Federal Circuit issued its opinion before the Court decided *KSR*, and *KSR* altered the obviousness landscape in at least two ways directly relevant here. *First*, the Court's opinion in *KSR* expressly eliminated the use of the Federal Circuit's teaching-suggestion-motivation test as the basic test

for obviousness. According to this Court, "[t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation." 550 U.S. at ___, 127 S. Ct. at 1741. And, in particular, with regard to that test's focus on "motivation," the Court noted that "[i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls." *Id.* at ___, 127 S. Ct. at 1741-42. Thus, the Court of Appeals' extensive focus on "motivation" in this case stands in sharp contrast to the approach articulated by this Court in *KSR*.

Second, the Court in *KSR* reaffirmed the principle that where combinations of known elements yield unexpected results, the unexpected nature of the results cuts against a finding of obviousness. To be sure, if "pursu[ing] the known options" leads to "anticipated success," it is likely a claimed invention is "the product not of innovation but of ordinary skill and common sense." *Id.* at ___, 127 S. Ct. at 1742; *see also id.* at ___, 127 S. Ct. at 1738 (combination is obvious "when it does no more than yield predictable results"). But, the Court expressly noted that when the combined elements work together in an "unexpected and fruitful manner," that surprising result supports a finding of nonobviousness. *Id.* at ____, 127 S. Ct. at 1740. At a minimum, this suggests that *KSR* adopted a quite different understanding of the importance that unexpected results play in the obviousness determination. In turn, that shows a "reasonable probability" that the Federal Circuit might decide this case differently after considering *KSR*.

The *KSR* opinion also offers further evidence confirming the need for a GVR order here. The Court's opinion directly referenced *DyStar*'s obviousness standard—the very standard that the court below relied on here. While acknowledging that in *DyStar* the Federal Circuit had "elaborated a broader conception of the TSM test," the Court expressly declined to rule on whether or not that standard met *KSR*'s demands, saying only that that "is a matter for the

Court of Appeals to consider in its future cases." 550 U.S. at ___, 127 S. Ct. at 1743. That consideration should have occurred here, and it should occur (with specific direction to do so) on remand.

In short, *KSR* changed the Federal Circuit's longstanding approach to obviousness, and the Federal Circuit's now-suspect pre-*KSR* teaching-suggestion-motivation framework was the *sole* underpinning to the Federal Circuit's decision in this case. Thus, there is a "reasonable probability" that, with a proper consideration of *KSR*, the Federal Circuit would come to a different result on obviousness. *See Chater*, 516 U.S. at 167. And, if it does, that change would almost certainly result in a different "ultimate outcome" below. *Id.*

C. The Equities Confirm The Need For A GVR Order

The equities of the case further confirm the appropriateness of a GVR order here. Indeed, the judges who dissented from the denial of rehearing expressly referred to the "exceptional importance" of the issues at stake here, and they were right. First, the Federal Circuit's decision is vitiating Pfizer's pediatric exclusivity for Norvaxc®, resulting in significant financial losses to Pfizer and its shareholders. Already, the decision below has enabled two generic products to compete against Pfizer's product, in derogation of Pfizer's exclusivity. Additional comopetitors might also be approved if the decision is not corrected, resulting in deeper financial losses. More importantly, though, the decision below does not merely affect Pfizer and Norvasc®. Rather, the decision below carries profound consequences for pharmaceutical research and development in general.

As the judges who dissented from the denial of rehearing noted, "[t]he panel decision changes the criteria as well as the analysis of patentability, with results of particular significance for their effect on the conduct of R&D, the costs of drug development, and the balance between generic access to established products and the incentive [for]

development of new products." App. 42a (Newman, J., dissenting). In essence, under the panel decision, an invention will not be patentable any time "that the invention was the result of routine experimentation," App. 48a (Lourie, J., dissenting), a troubling result in that "methodical experimentation is fundamental to scientific advance, and particularly for biological and medicinal products, where small change[s] can produce large differences," App. 42a (Newman, J., dissenting). In fact, as Judge Rader observed in dissent, the "decision calls into question countless pharmaceutical patents, which in turn could have a profoundly negative effect on investments into the design and development of new life-saving pharmaceuticals." App. 51a (Rader, J., dissenting).

In language directly on point here, the panel opinion below, quoting *DyStar*, observed that "[o]bviousness is a complicated subject requiring sophisticated analysis" based on "careful reading of the full text of a group of related precedents." App. 27a (internal quotation marks omitted). Without "careful, candid, and complete legal analysis," the court continued, "much confusion about the law arises." App. 27a (internal quotation marks omitted). Unfortunately, the Court of Appeals failed to heed its own admonition and failed to provide a "complete legal analysis" that included consideration of *KSR*, this Court's most recent pronouncement on the subject. GVR is particularly appropriate in this light.

II. IF THE COURT OF APPEALS' DECISION IS NOT REVIEWED PRIOR TO SEPTEMBER 25, 2007, THE CASE WILL BECOME MOOT, AND IN THAT EVENT THE PETITION SHOULD BE GRANTED WITH DIRECTIONS TO VACATE THE COURT OF APPEALS' DECISION UNDER *United States v. Munsingwear* AND *U.S. Bancorp Mortgage Corp. v. Bonner Mall Partnership*

As we have shown in Section I, the Court of Appeals' invalidation of Pfizer's '303 patent has profound implications for virtually all pharmaceutical patents. The three opinions dissenting from the denial of rehearing *en banc* in the Federal Circuit confirm that the issue presented here is one of "exceptional importance" (App. 46a (Lourie, J., dissenting)), which "calls into question countless pharmaceutical patents, which in turn could have a profoundly negative effect on investments into the design and development of new life-saving pharmaceuticals." App. 51a (Rader, J., dissenting). On those terms alone, the decision below would merit plenary review by this Court.

As a practical matter, though, it will be all but impossible for this Court to decide this case on full briefing and argument. The Federal Circuit's denial of rehearing—in which it failed to reconsider its decision in light of *KSR*—came on May 21, 2007. The '303 patent expired on March 25, 2007, however, which means that the only rights Pfizer has left are its rights to six additional months of pediatric exclusivity. Because the period of pediatric exclusivity associated with the '303 patent will expire on September 25, 2007 (the Tuesday before the first Monday in October), this case will become moot if it is not reviewed before then. Thus, Pfizer is asking this Court to issue a GVR order—and an expedited one, at that—so that the Federal Circuit can properly reconsider its decision in light of *KSR* before the issue becomes an academic one.

If the Court cannot dispose of this petition before September 25, however, then Pfizer requests that the Court grant the petition and vacate the judgment of the Federal Circuit pursuant to *United States v. Munsingwear, Inc.*, 340 U.S. 36 (1950) and *U.S. Bancorp Mortgage Co. v. Bonner Mall Partnership*, 513 U.S. 18 (1994). Under those decisions, the "established practice of the Court in dealing with a civil case from a court in the federal system which has become moot while on its way here or pending our decision on the merits is to reverse or vacate the judgment below and remand with a direction to dismiss." *Munsingwear*, 340 U.S. at 39. "That procedure clears the path for future relitigation of the issues between the parties and eliminates a judgment, review of which was prevented through happenstance. When that procedure is followed, the rights of all parties are preserved; none is prejudiced by a decision which in the statutory scheme was only preliminary." *Id.* at 40.

There is no question but that the mootness here would be caused by the "happenstance" of the statutory expiration of Pfizer's patent rights, combined with the timing of both this suit and the Federal Circuit's decision not to rehear the case. When combined with Pfizer's vigilance in filing this petition, it cannot possibly be said that Pfizer "caused the mootness by voluntary action," disentitling it from the equitable relief of vacatur under *U.S. Bancorp*, 513 U.S. at 24. "[M]ootness by happenstance provides sufficient reason to vacate." *Id.* at 25 n.3.*

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* Under the FDA's April 18, 2007 letter to all ANDA applicants/holders for amlodipine besylate tablets, issued after the panel decision in this case, the FDA concluded that it could not approve any ANDAs for amlodipine besylate (except for Mylan's already-approved ANDA) until the Federal Circuit issued its mandate. *See Mylan Labs. v. Leavitt*, ___ F. Supp. 2d ___, 2007 WL 1241884 (D.D.C. April 30, 2007). Upon denying rehearing and rehearing *en banc* in this case on May 21, 2007, the Federal Circuit ordered that the mandate issue *instanter* (App. 40a),

Indeed, the equities would all point to vacatur in the case of mootness. In two challenges from other generic manufacturers, two other district courts have upheld the '303 patent against obviousness challenges, with detailed findings of fact to support those judgments. *See Pfizer Inc. v. Mylan Labs., Inc.*, No. 02:02CV1628, 2007 WL 654274 (W.D. Pa. Feb. 27, 2007), *appeal docketed*, No. 2007-1194 (Fed. Cir. Mar. 6, 2007); *Pfizer Inc. v. Synthon Holdings BV*, No. 1:05CV39, 2006 WL 2553370 (M.D.N.C. Aug. 31, 2006), *appeal docketed*, No. 2007-1045 (Fed. Cir. Nov. 9, 2006). Those manufacturers have claimed that the collateral-estoppel authority of the March 22, 2007 panel decision in this case resolves their appeals from those judgments and allows them to bring to market generic versions of Norvasc®. In the case of Mylan, which has already brought a generic version to market based on this authority, that company has unfairly asserted, in a motion for summary reversal in the Federal Circuit, that the collateral estoppel effect of the obviousness decision below bars Pfizer from suing them even for the infringement damages suffered by Pfizer prior to patent expiration. *See Pfizer Inc. v. Mylan Labs., Inc.*, No. 2007-1194 (Fed. Cir. Mar. 29, 2007). It would be inequitable to allow the judgment in this case to stand, thereby potentially giving rise to assertions of collateral estoppel against Pfizer, were this case to become moot by the happenstance of the passage of time. *See United States v. Hamburg-Amerikanische Packet-Fahrt-Actien Gesellschaft*, 239 U.S. 466, 478 (1916) ("the ends of justice exact that the judgment below should not be permitted to

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and Apotex launched its generic amlodipine besylate on May 24, 2007. Pfizer has asked this Court to order that mandate recalled and stayed. If that does not occur, it is possible that this case became moot with the issuance of the Federal Circuit's mandate; in that event, the judgment here should be vacated, as the case for vacatur based on mootness by happenstance is no less strong under those circumstances.

stand when, without any fault of the [petitioner], there is no power to review it upon the merits").

Viewing the issue more broadly, the equities also counsel against leaving the judgment of the Court of Appeals on the books as binding precedent. For one, as noted above and by the dissenters from the denial of rehearing *en banc*, the decision has profound and negative consequences for the patentability of novel pharmaceutical compositions when the ground for patentability is found in developments other than therapeutic effectiveness (such as found here in the superior manufacturing qualities of amlodipine besylate). The fact that this decision was reached without the benefit of considering this Court's intervening decision in *KSR* makes the case for vacatur here even more compelling; district courts should not be forced to follow the decision below as precedent, particularly when there are substantial questions regarding its validity in view of *KSR*. Vacatur here will therefore clear the path for this issue to be litigated again in future cases, where appellate review will not be impeded by the happenstance of patent expiry, and where the courts hearing the cases will have the full opportunity to consider *KSR*, this Court's most recent pronouncement on the statutory doctrine of obviousness. In that light, if "the demands of 'orderly procedure' cannot be honored" in this case, then "the public interest is best served by granting relief." *U.S. Bancorp*, 513 U.S. at 27 (quoting *Munsingwear*, 340 U.S. at 41) (internal citation omitted).

CONCLUSION

The petition should be granted, and the judgment of the Court of Appeals vacated.

Respectfully submitted,

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May 29, 2007

APPENDIX

UNITED STATES COURT OF APPEALS, FEDERAL CIRCUIT.

PFIZER, INC.,
Plaintiff-Appellee,

v.

APOTEX, INC. (FORMERLY KNOWN AS TORPHARM, INC.),
Defendant-Appellant.

NO. 2006-1261.

DECIDED: MARCH 22, 2007.

Before MICHEL, Chief Judge, MAYER, and LINN, Circuit Judges.

MICHEL, Chief Judge.

Pfizer Inc. filed suit against Apotex, Inc. (formerly known as TorPharm, Inc.) in the United States District Court for the Northern District of Illinois on July 30, 2003, alleging that, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Apotex's filing with the United States Food and Drug Administration ("FDA") of its Abbreviated New Drug Application ("ANDA") No. 76-719 seeking approval to commercially sell amlodipine besylate tablets (2.5 mg, 5 mg, and 10 mg strengths) before the expiration of the term of U.S. Patent No. 4,879,303 ("the 303 patent") to Pfizer, infringed claims 1-3 of the 303 patent. The ANDA product sought to be approved by Apotex is a generic version of Pfizer's amlodipine besylate drug product, which is commercially sold in tablet form in the United States under the trademark Norvasc® . Norvasc® is approved by the FDA for treating

hypertension and chronic stable and vasospastic angina. The 303 patent, entitled "Pharmaceutically Acceptable Salts," is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") with respect to the Norvasc® drug product in accordance with 21 U.S.C. § 355(b)(1). Apotex certified in ANDA No. 76-719 that it believed the 303 patent was invalid and unenforceable, and sought approval to market and sell its amlodipine besylate tablets before September 25, 2007 (i.e., the expiration date of the 303 patent plus an additional six months of pediatric exclusivity) pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

In its answer to Pfizer's complaint, Apotex denied infringement and counterclaimed for declaratory judgments that the claims of the 303 patent are invalid for anticipation and obviousness, and that the 303 patent is unenforceable due to Pfizer's alleged inequitable conduct before the United States Patent and Trademark Office ("USPTO"). Prior to trial, however, Apotex stipulated that its ANDA product contains each limitation of claims 1-3 of the 303 patent, and that if the 303 patent were upheld as valid and enforceable, its ANDA product would literally infringe those claims.

Following a bench trial, the district court entered a final judgment on January 29, 2006 for Pfizer and against Apotex on Apotex's request for declaratory judgments that the claims of the 303 patent are invalid or unenforceable. Based on the stipulation, the trial court found infringement. The district court then ordered that the effective date of any approval of Apotex's ANDA No. 76-719 shall not be earlier than September 25, 2007, and enjoined Apotex from making, using, offering to sell, selling, or importing into the United States any product comprising amlodipine besylate covered by (or the use of which is covered by) the claims of the 303 patent until September 25, 2007. *Pfizer Inc. v. Apotex, Inc.*, No. 03C 5289 (N.D.Ill. Jan. 29, 2006).

Pfizer dismissed its claim of willful infringement against Apotex by a Stipulation and Order dated January 23, 2006. Apotex now appeals from the district court's final judgment, challenging the rulings as to validity and enforceability. Because the district court erred in holding that the subject matter of claims 1-3 of the 303 patent would not have been obvious, we reverse. We therefore do not address Apotex's assertion that it had proven that Pfizer engaged in inequitable conduct before the USPTO during prosecution of the 303 patent.

I. BACKGROUND

A.

Norvasc® contains amlodipine besylate. The active ingredient found in Norvasc® is 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, commonly referred to as amlodipine. Amlodipine is a member of a class of compounds referred to as dihydropyridines. Active drug molecules, such as amlodipine, are frequently made into pharmaceutically-acceptable acid addition salts to improve their bioavailability. Amlodipine besylate [1] is an acid addition salt form of amlodipine, formed from the reaction of amlodipine, a weak base, and benzene sulphonic acid.

Pfizer's Discovery Chemistry group, located in Sandwich, England, invented amlodipine and discovered its anti-hypertensive and anti-ischemic pharmacological properties prior to 1982. Pfizer filed a patent application in the United Kingdom on March 11, 1982 specifically claiming amlodipine. A U.S. counterpart application claiming priority

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[1] Besylate is referred to in the art interchangeably as benzene sulphonate, benzenesulphonate, or benzene sulfunate.

from the U.K. application issued as U.S. Patent No. 4,572,909 ("the 909 patent") on February 25, 1986.[2] The 909 patent claims certain dihydropyridine compounds and their pharmaceutically-acceptable acid addition salts. The 909 patent discloses that the pharmaceutically-acceptable acid addition salts of amlodipine "are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts," and that the preferred salt is maleate.[3] 909 patent col.2 ll.3-10.

Meanwhile, on or about July 14, 1982, the Discovery Chemistry group recommended that amlodipine be developed as a commercial drug product. By this time, Pfizer had made several acid addition salts of amlodipine, including the maleate, fumarate, salicylate, hydrochloride, and methane sulphonate forms. The Discovery Chemistry group designated amlodipine maleate as the drug substance for development.

On or about August 11, 1982, the project of formulating a commercial drug product was assigned to Dr. James Wells, a manager in Pfizer's Pharmaceutical Research and Development Department, who was assisted by Mr. Edward Davison, a member of the same group. By April 24, 1984, Dr. Wells identified a formulation for amlodipine

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[2] The 909 patent was subject to an appeal before this court in *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361 (Fed.Cir.2004). There, this court held that the term of the 909 patent as extended under the patent term restoration provision of the Hatch-Waxman Act covers amlodipine and any salt or ester as claimed in claims 1, 7, and 8. *Id.* at 1367.

[3] We recognize that hydrochloride and hydrobromide are not technically anions. However, since the patentee chose to be his own lexicographer, we will refer to these two acids as anions for purposes of this opinion. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed.Cir.2005) (en banc).

maleate that produced "excellent capsules." In attempting to produce a direct compression tablet product of an amlodipine maleate formulation, however, Dr. Wells encountered two problems: (1) chemical instability of the amlodipine maleate, and (2) stickiness of the tablet blend of amlodipine maleate. Chemical stability refers to the resistance of a drug compound to chemical breakdown, while stickiness refers to the adherence of the drug substance, in formulation, to manufacturing equipment, such as the punch faces of a tablet-making press.

To solve the problems of the tablet form of amlodipine maleate, Dr. Wells suggested that other amlodipine salts be made and tested. In a memo dated April 24, 1984, Dr. Wells acknowledged the difficulty in stickiness and stability he was experiencing in attempting to make a tablet formulation of amlodipine maleate and stated that, by changing from the maleate salt to the free base of amlodipine or another acid addition salt, "many of the stability problems would disappear." Dr. Wells identified six alternative anions, i.e., hydrochloride, methane sulphonate, benzene sulphonate, lactate, succinate, and acetate, as potential anions with which to create acid addition salt forms of amlodipine. He also eventually added the tosylate anion to this group. Dr. Wells testified at trial that he selected these candidates based on their differing structures and properties, but could not explain why three of the seven alternative anions were members of the same class of sulphonic acids.

Mr. Davison testified at trial that he tested these amlodipine acid addition salt forms as well as amlodipine maleate and the free base for solubility, pH, hygroscopicity, and stickiness. Another researcher, Dr. Robin Platt, an analytical chemist at Sandwich, was brought in to test the stability of the amlodipine acid addition salts. Dr. Platt subjected the maleate, acetate, succinate, besylate, mesylate, and eventually the tosylate, salicylate, and hydrochloride salt forms of amlodipine to thin-layer chromatography to determine the number and amount of degradants found in the

various amlodipine salts, and compiled a ranking thereof based upon the stability of each salt formulation.

Dr. Platt's findings were communicated to Dr. Wells via memorandum on or about October 9, 1984, wherein Dr. Platt reported that the besylate salt "showed a much improved stability profile over the maleate in all cases." On October 11, 1984, Dr. Wells recommended via memorandum to Dr. J.R. Davidson, a deputy of Pfizer's Pharmaceutical Research and Development Department, that the amlodipine maleate salt be replaced with amlodipine besylate for the commercial amlodipine tablet product based on Dr. Platt's memo and Mr. Davison's test results.

By April 30, 1985, both amlodipine maleate and amlodipine besylate were undergoing human testing in clinical trials. Pfizer scientists predicted that the capsule form of amlodipine maleate would have a shelf life of three years, but that "poor stability of amlodipine maleate tablet formulations" precluded commercialization. On the other hand, the scientists noted that amlodipine besylate tablet formulations exhibited "clear superiority" in their processing characteristics, particularly non-stickiness, and in stability. Capsule formulations of amlodipine besylate had not yet been produced, but work on this project was "expected to be straightforward."

On April 4, 1986, Pfizer filed a patent application to amlodipine besylate in the U.K., which eventually issued as U.K. Patent No. 160833. On May 5, 1986, Pfizer submitted a supplement to the FDA stating that the dosage form anticipated for commercial use would be a tablet of amlodipine besylate and that all future clinical trials with amlodipine would use this new formulation. In the supplement, Pfizer stated, "We feel that the change in salt form is justified since benzenesulfonate is a commercially acceptable salt, as exemplified by the tranquilizer mesoridazine (Serentil)." In support of the use of the

besylate salt form of amlodipine, Pfizer submitted a summary of the acute oral toxicity of amlodipine besylate and amlodipine maleate in rats and a comparison of the effects of both the besylate and maleate forms on blood pressure and heart rate of dogs. Pfizer stated that the results showed that there was no quantitative difference in efficacy between equivalent doses of amlodipine besylate tablets or capsules and amlodipine maleate capsules. In addition, Pfizer submitted a pharmacokinetic report and interim clinical summary showing that amlodipine besylate tablets and amlodipine maleate capsules were bioequivalent and had comparable safety and toleration when administered to healthy human volunteers.

On March 25, 1987, Pfizer filed a U.S. application (serial no. 07/030,658) to amlodipine besylate claiming priority from the U.K. application. During prosecution, the examiner initially rejected all claims of the application as obvious over the 909 patent in view of U.S. Patent 4,032,637 to Spiegel (1977) ("Spiegel") and U.S. Patent 3,816,612 to Schmidt (1974) ("Schmidt"). The examiner noted that Schmidt discloses that aryl sulphonic acid salts, which include besylate, are superior to the preferred maleate of the '909 patent, while Spiegel provides an example of a pharmaceutical compound wherein the besylate form is specifically identified as the preferred embodiment. In response to the rejection, Pfizer argued that the besylate salt,

> while *not* the most soluble salt, has many other advantages not possessed by other acid addition salts.... [I]n addition to having good solubility, [the besylate salt] is unique in imparting to the product good stability, nonhygroscopicity and good processability. For one salt to have all of these outstanding features is not suggested or taught in the art, and would require extensive experimentation to find.

The examiner, however, maintained the rejection, stating that "these qualities are basic considerations by a person skilled in the art for selecting a suitable pharmaceutical salt" as evidenced by Berge, "Pharmaceutical Salts," *J. Pharm. Sci.*, 66(1):1-19 (Jan.1977) ("Berge"). Table 1 of Berge shows 53 FDA-approved, commercially marketed anions, including benzene sulphonate, that are useful for making pharmaceutically-acceptable salts, and lists the relative frequency of which each was used as a percentage based on the total number of anions or cations in use through 1974. Berge discloses that benzene sulphonate had a frequency of use of 0.25%.

In response to a final obviousness rejection by the Examiner, Pfizer filed a continuation application (serial no. 07/256,938) and abandoned the original application. Along with the continuation application, Pfizer submitted a preliminary amendment and statement, and a declaration under 37 C.F.R. § 1.132 by Dr. Wells dated October 3, 1988 ("Wells Declaration"). In the statement, Pfizer argued that the Wells Declaration demonstrated that the besylate salt of amlodipine possessed "*all* the desired characteristics necessary for a medicinal agent" and that it would not have been obvious "that only the besylate salt of amlodipine would have all the necessary properties for a commercial product." Pfizer argued that choosing an appropriate salt is a very difficult task "since each salt imparts unique properties to the parent compound" and that one skilled in the art would "conclude that the besylate salt of amlodipine is a unique compound and not an obvious one." The Wells Declaration stated that the besylate salt of amlodipine was "found to possess a highly desirable combination of physicochemical properties," including good solubility, stability, non-hygroscopicity, and processability, which properties are "unpredictable both individually and collectively."

The continuation application was allowed and issued as the 303 patent on November 7, 1989. The first three claims of the 303 patent are reproduced here:

1. The besylate salt of amlodipine.

2. A pharmaceutical composition comprising an anti hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically-acceptable diluent or carrier.

3. A tablet formulation comprising an anti-hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.

Norvasc® was launched as a commercial product by Pfizer in the U.S. in November 1992.

B.

From January 11, 2006, to January 18, 2006, the district court conducted a bench trial on the issues of (1) whether the claims of the 303 patent were anticipated by the disclosure of the 909 patent, (2) whether the 303 patent was invalid for obviousness, and (3) whether the claims of the 303 patent were unenforceable due to inequitable conduct before the USPTO. On January 18, 2006, the district court stated its findings and conclusions pursuant to Fed.R.Civ.P. 52(a) orally in open court. *Bench Order Tr.* 1-28, January 18, 2006. The district court concluded that Apotex failed to meet its burden of proving invalidity or inequitable conduct by clear and convincing evidence.

The district court first addressed the issue of invalidity by anticipation, finding that while the 909 patent claims a genus of pharmaceutically-acceptable salts of amlodipine that encompasses amlodipine besylate, the 909 patent does not as a matter of law disclose it. The district court held that since the 909 patent does not list the species

of a salt made from benzene sulphonate, it does not anticipate the claims of the 303 patent.

With regard to obviousness, the district court rejected Apotex's argument that the 909 patent in view of the Berge article (and other prior art) rendered the invention of the claims of the 303 patent obvious. The district court first found that a person of ordinary skill in the art would have a bachelor's degree in pharmaceutical science or analytical chemistry, and some experience in drugs and drug preparation. The district court concluded that the Berge article does not direct the skilled artisan to create the besylate salt of amlodipine because Berge discloses that benzene sulphonate was used only at a frequency of 0.25%, or 1 out of every 400 drugs, prior to 1974. The district court noted that the examiner must have considered the Berge article since it was cited in the 303 patent, yet the examiner ultimately determined that the claims of the 303 patent were not obvious in view of this reference.[4] Further, the district court stated that there would be no expectation of success in making a besylate salt of amlodipine because, as Berge teaches and expert testimony on both sides accepted, "There is no reliable way of predicting the influence of a particular salt species on the behavior of a parent compound." *Bench Order Tr.* 23:3-6.

The district court also stated that the besylate salt of amlodipine was unexpectedly superior to the amlodipine salts of the prior art. Specifically, the district court stated that,

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[4] The trial transcript reads, "The patent examiner cannot [sic] have been aware of the Berge article as it was specifically noted and cited in the 303 patent itself. As such, the Court could not possibly find by clear and convincing evidence that the article and its teachings could not have been considered by the patent [sic] when ultimately determining whether the 303 patent was obvious...." *Bench Order Tr.* 22:16-22. We interpret this passage in the only way that makes sense-that the Examiner did consider the Berge reference during prosecution. While oral bench rulings are certainly authorized, they may be ill-advised in a case of this complexity.

while amlodipine besylate was not superior to amlodipine maleate "in every category," it nonetheless "clearly and unexpectedly illustrates a superior combination of properties when compared to what was suggested in the preferred preparation"-- ostensibly the amlodipine maleate disclosed as the preferred embodiment of the 909 patent. These properties included good solubility, stability, non-hygroscopicity, and processability (non-stickiness). The district court found that amlodipine besylate exhibited at least a solubility exceeding 1.0 mg/ml, which the court stated is the desirable solubility factor for a commercial product, and that the 303 patent listed the besylate salt form of amlodipine as the most stable salt form out of eight salts tested, with the maleate salt form being sixth on the list.

The district court also rejected Apotex's argument that amlodipine besylate is actually hygroscopic rather than non-hygroscopic as disclosed in the 303 patent. Apotex asserted that amlodipine besylate attracts water because it (1) can exist as a hydrate, (2) may have water within its crystalline structure, and (3) can have water on its surface at extended temperatures and humidity. The district court stated that while each of these facts is true, each was entirely unenlightening because hygroscopicity per se was not a critical factor. Instead, the district court emphasized that the maleate salt of amlodipine underwent a Michael addition reaction when exposed to water, creating at least ten degradation products making amlodipine maleate unsuitable at least in tablet form for medicinal purposes, whereas the amlodipine besylate did not undergo the same reaction. Lastly, the district court found that Pfizer conducted extensive tests for processability of the amlodipine besylate by manufacturing tablets on conventional tablet-making machinery and measuring the amount of product sticking to the punch face after each manufacturing run. The district court concluded that the tests showed that amlodipine besylate was sufficiently non-sticky so as to be commercially processable and less sticky than the maleate form.

Besides evidence of superiority provided in the 303 patent itself, the district court pointed to another "objective consideration" in determining that amlodipine besylate was not obvious over the prior art: "Pfizer would not have changed from the maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason." *Bench Order Tr.* 23:16-21. For all these reasons, the district court held that the claims of the 303 patent were not proven invalid for obviousness.

Next, the district court rejected Apotex's claim that Pfizer engaged in inequitable conduct before the USPTO in violation of its duty of candor and 37 C.F.R § 1.56. Apotex argued that Pfizer made several material misrepresentations to the USPTO during prosecution of the application leading to the 303 patent, including misrepresenting the solubility, stability, and hygroscopicity of amlodipine besylate and misrepresenting the number of tablets tested for processability both in the patent application and in the Wells Declaration. Specifically, Apotex asserted that Pfizer (1) fraudulently identified the solubility of amlodipine besylate in its application for patent as 4.6 mg/ml where internal Pfizer documents show the solubility to actually be 3.5 mg/ml; (2) fraudulently claimed in the application to have tested over a thousand tablets for stickiness where internal Pfizer documents show varying numbers up to only 150 tablets were actually tested; and (3) fraudulently ranked the respective stabilities of the various salt forms of amlodipine in an ordinal-rather than quantitative-fashion so as to conceal from the USPTO that the stability differences between the besylate, tosylate, and mesylate salt forms of amlodipine were actually very minor.

The district court first determined that none of these alleged misrepresentations were either material or false. In this regard, the court stated that whether the solubility of amlodipine besylate is 4.6 mg/ml as identified in the 303 patent or 3.5 mg/ml as identified in internal Pfizer documents

was at most a minor discrepancy given that any solubility over the critical 1.0 mg/ml level was sufficient solubility to meet the standards of a drug company seeking to produce a commercial drug. As for stability, the district court found that amlodipine besylate was far more stable than amlodipine maleate, which as described above undergoes the undesirable Michael addition reaction. Second, the district court held that Apotex failed to show intent to deceive by clear and convincing evidence. Indeed, the court found "precious little evidence at all" showing an intent to deceive, stating that "[w]hile it is clear that Pfizer was eager to extend the patent life of its amlodipine compound, such a desire does not rise to the level of fraudulent conduct." *Bench Order Tr.* 25:24-26:1.

On January 29, 2006, the district court entered a final judgment in favor of Pfizer and against Apotex on Pfizer's claim of infringement as well as on Apotex's counterclaims alleging and seeking declarations of invalidity and unenforceability of the 303 patent. The district court also ordered that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Apotex's ANDA No. 76-719 shall not be earlier than September 25, 2007, and pursuant to 35 U.S.C. § 271(e)(4)(B), enjoined Apotex, its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with it, from engaging in the manufacture, use, offer for sale, or sale within the U.S., or importation into the U.S. of any product comprising amlodipine besylate covered by, or the use of which is covered by, the claims of the 303 patent until September 25, 2007. *Pfizer Inc. v. Apotex, Inc.*, No. 03C 5289 (N.D.Ill. Jan. 29, 2006). On February 17, 2006, Apotex filed a timely notice of appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

A.

Apotex appeals the district court's final judgment that it failed to prove by clear and convincing evidence that the invention of claims 1-3 of the 303 patent would have been obvious and are therefore invalid, and the district court's finding that Apotex failed to prove Pfizer committed inequitable conduct before the USPTO. Because the district court erred in holding non-obvious the invention of claims 1-3 of the 303 patent, we reverse the district court's judgment. Since we hold that claims 1-3 are invalid for obviousness, we need not and do not address Apotex's assertion that Pfizer engaged in inequitable conduct before the USPTO during prosecution of the 303 patent.

On appeal from a bench trial, this court reviews the trial court's conclusions of law de novo and findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed.Cir.2004). The ultimate conclusion of whether a claimed invention would have been obvious is a question of law reviewed de novo based on underlying findings of fact reviewed for clear error. *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed.Cir.1997). A factual finding is clearly erroneous if, despite some supporting evidence, "the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395, 68 S.Ct. 525, 92 L.Ed. 746 (1948).

B.

The district court held that Apotex had established a prima facie case of obviousness because the patent examiner initially rejected the claims to amlodipine besylate for obviousness. Specifically, the district court stated, "The

303 patent's file wrapper shows that the examiner originally rejected the claimed invention because of obviousness. Under these circumstances, of course, the Court must accept that the defendant has made a prima facie showing on this question." *Bench Order Tr.* 21:20-24. The district court's ruling must be rejected, not only because it is legally incorrect, but also because it may reflect a serious misconception regarding the proper burden of proof each party bears in a patent litigation.

Our case law consistently provides that a court is never bound by an examiner's finding in an ex parte patent application proceeding. *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1555 (Fed.Cir.1985). Thus, it can never be the case that an examiner's interim finding of prima facie obviousness renders the claims of an issued patent prima facie obvious. Instead, deference to the decisions of the USPTO takes the form of the presumption of validity under 35 U.S.C. § 282. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1329 (Fed.Cir.2000). That is, by statute a patent is valid upon issuance, 35 U.S.C. § 282, and included within the presumption of validity is a presumption of non-obviousness. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 714 (Fed.Cir.1984). Since we must presume a patent valid, the patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence. [5] That burden of proof never shifts to the patentee to prove validity. *Hybritech Inc. v. Monoclonal*

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[5] The "clear and convincing" standard is an intermediate standard which lies somewhere in between the "beyond a reasonable doubt" and the "preponderance of the evidence" standards of proof. *Addington v. Texas*, 441 U.S. 418, 425, 99 S.Ct. 1804, 60 L.Ed.2d 323 (1979); *see also SSIH Equip. S.A. v. United States Int'l Trade Comm'n*, 718 F.2d 365, 380-81 (Fed.Cir.1983) (Nies, J., additional views). Although an exact definition is elusive, "clear and convincing evidence" has been described as evidence that "place[s] in the ultimate factfinder an abiding conviction that the truth of its factual contentions are highly probable." *Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433, 81 L.Ed.2d 247 (1984) (internal quotations omitted).

Antibodies, Inc., 802 F.2d 1367, 1375 (Fed.Cir.1986). "The presumption [of validity] remains intact and [the burden of proof remains] on the challenger throughout the litigation, and the clear and convincing standard does not change." *Id.*

It is true that once a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence. *See Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1216 (Fed.Cir.1998) (citing *Hybritech*, 802 F.2d at 1376); *Cable Elec. Prods. Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1022 (Fed.Cir.1985) ("[I]f evidence is presented establishing a prima facie case of invalidity, the opponent of invalidity must come forward with evidence to counter the prima facie challenge to the presumption of section 282."). But, all that means is that even though a patentee never *must* submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity-what we call a prima facie case-the patentee "would be well advised to introduce evidence sufficient to rebut that of the challenger." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1570 (Fed.Cir.1986).

However, this requirement does not "in substance shift the burden of persuasion," *Cable Elec.*, 770 F.2d at 1022, because "the presumption of validity remains intact and the ultimate burden of proving invalidity remains with the challenger throughout the litigation." *Mas-Hamilton Group*, 156 F.3d at 1216; *see also Innovative Scuba Concepts, Inc. v. Feder Indus., Inc.*, 26 F.3d 1112, 1115 (Fed.Cir.1994); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 287 (Fed.Cir.1985). The trial court has the responsibility to determine whether the challenger has met its burden by clear and convincing evidence by considering the totality of the evidence, including any rebuttal evidence presented by the patentee. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed.Cir.1983).

The *basis* (as opposed to the mere existence) of an examiner's initial finding of prima facie obviousness of an issued patent is therefore, at most only one factual consideration that the trial court must consider in context of the totality of the evidence "in determining whether the party asserting invalidity has met its statutory burden by clear and convincing evidence." *Fromson,* 755 F.2d at 1555. It does not, however, lessen or otherwise affect the burden of proof, nor does it require that unless the patentee introduces evidence of secondary considerations to establish non-obviousness, the patent challenger will necessarily prevail.

C.

The underlying factual determinations made by the trial court that this court must review for clear error include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of non-obviousness. *Graham v. John Deere Co.,* 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). We start by noting that the parties stipulated to many of the facts, but disagree as to the ultimate legal outcome of obviousness based upon those facts. The parties do not dispute that benzene sulphonate was known in the art at the time of the inventions claimed in the 909 and 303 patents. Pfizer admitted that several publications, including the Berge article, were prior art to claims 1-3 of the 303 patent and pertinent to the problem the inventors sought to overcome. Neither party disputes the district court's characterization of the ordinarily skilled artisan.

Further, there is really no dispute as to the scope of the 909 patent and the differences between it and the claimed invention. The 909 patent specifically states that the pharmaceutically-acceptable salts of amlodipine "are those formed from acids which form non-toxic acid addition salts

containing pharmaceutically-acceptable anions." 909 patent col.2 ll.3-6. The 909 patent lists a genus of pharmaceutically-acceptable anions "such as the hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate." 909 patent col.2 ll.6-9. The only examples of acid addition salts of amlodipine are maleates. The 909 patent does not expressly disclose the benzene sulphonate anion nor salts formed from benzene sulphonic acid or a larger class of sulphonic acids in general. But, while neither the claims nor the written description of the 909 patent expressly disclose amlodipine besylate or the benzene sulphonate anion, neither do they exclude amlodipine besylate or the benzene sulphonate anion. Rather, the only limitations placed on the anion are that it is pharmaceutically-acceptable, and that in salt form, it is able to produce a non-toxic acid addition salt. Thus, as the district court found and the parties agree, the 909 patent claims literally encompass amlodipine besylate.

By statute, a claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Subsumed within the *Graham* factors is a subsidiary requirement articulated by this court that where, as here, all claim limitations are found in a number of prior art references, the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so. *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed.Cir.2006); *Velander v. Garner*, 348 F.3d 1359, 1363 (Fed.Cir.2003). Here, the parties vigorously disagree.

A difficulty in the district court's opinion arises because, in assuming a prima facie case of obviousness, the

district court did not fully address whether Apotex showed by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references relied on, especially the 909 patent and Berge, to achieve the claimed invention. However, the district court's omission in this case is harmless error because evidence of record easily satisfies us that a reasonable fact-finder could only conclude that Apotex has shown by clear and convincing evidence that the skilled artisan would indeed have been so motivated to combine the prior art to produce the besylate salt of amlodipine. The record also satisfies us that, contrary to the district court's finding, a reasonable fact-finder could only conclude that the skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine for the reasons elaborated, post.

Motivation to Combine Prior Art References to Achieve the Claimed Invention

Pfizer does not argue that there was no motivation to combine the prior art references per se. Rather, Pfizer argues that (1) the 909 patent does not suggest or motivate the skilled artisan to make amlodipine besylate because none of the anions listed in the 909 patent have a cyclic structure as does besylate, and (2) even if the 909 patent were combined with Berge, the skilled artisan would not have been motivated to make amlodipine besylate because Berge shows that besylate was actually one of the most rarely used anions in the pharmaceutical industry, as only 0.25% of approved drugs as of 1974 were besylate salts. Finally, Pfizer asserts that other prior art references relied upon by Apotex are not relevant because the examples of besylate salts disclosed in these references are limited to pharmaceuticals unrelated to amlodipine.

We reject Pfizer's first argument, since a suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to

be found explicitly in the prior art references sought to be combined, but rather "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *DyStar,* 464 F.3d at 1361; *see also Ormco Corp. v. Align Tech., Inc.,* 463 F.3d 1299, 1307-08 (Fed.Cir.2006). In other words, it is irrelevant that none of the anions specifically listed in the 909 patent have a cyclic structure, because the motivation to make amlodipine besylate here is gleaned not only from the prior art as a whole rather than the 909 patent alone, but also from the nature of the problems encountered with the amlodipine maleate tablet formulations sought to be solved by the inventors of the 303 patent. In this regard, testimony of record evidences that one skilled in the art would have been motivated to choose an anion having a different structure than that of maleate. The maleate salt ion is acyclic and consists of a double bond between the carbon atoms, whereas the besylate salt ion is cyclic and lacks the same double bond. Early in development, Pfizer discovered that amlodipine maleate was susceptible to degradation from a Michael addition reaction in which the double bond of maleate underwent an addition reaction causing the formation of degradation products. Apotex avers that unrebutted testimony from its expert, which we find compelling, supports an inference that the skilled artisan actually would have been encouraged, rather than discouraged, to choose an anion without the same double bond, such as benzene sulphonate, in order to avoid the Michael addition reaction. Thus, the fact that none of the anions listed in the 909 patent have a cyclic structure is hardly dispositive to the question of whether the skilled artisan would have been motivated to combine the prior art references to achieve amlodipine besylate.

We similarly are not persuaded by Pfizer's second argument, as clear and convincing evidence shows that a skilled artisan would have been motivated to combine the 909 patent and Berge to make amlodipine besylate. Pfizer's expert, Dr. Anderson, testified that there were an unlimited

number of anions, many of which could be used to form pharmaceutically-acceptable acid addition salts. Yet a reasonable fact-finder could not accept Dr. Anderson's testimony that the number of acceptable anions was "unlimited." Of course, new salts can always be made or attempted. However, irrefutable evidence shows that a skilled chemist at the time would simply make *known* pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time. Indeed, Mr. Davison, an inventor of the 303 patent, testified that it "would have been a mistake" to choose a novel anion. Rather, "part and parcel of pharmaceutically accepted[ ] was to look in pharmacopoeias and compendia" to find an anion having "precedence for use within the pharmaceutical industry." Dr. Anderson similarly admitted in his testimony that it would have been logical to use Berge's list of FDA-approved anions to produce a drug formulation:

> Court: What if I sic my phalanx of zealous scientists on that list and then come up with a product. Would that be a logical thing for me to do? The Witness: It would be logical to try that.

This is true especially given the fact that the genus of FDA-approved anions at the time was small, i.e., only 53. That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as "rarely used." *See* Berge, Table 1 (showing that 40 out of 53 anions were used in less than 1% of drugs and 23 out of 53 were used in 0.25% or less of drugs).

But the outcome of this case need not rest heavily on the size of the genus of pharmaceutically-acceptable anions disclosed by Berge because clear and convincing evidence establishes that, out of the list of 53 anions, one of ordinary skill in the art would have favorably considered benzene

sulphonate because of its known acid strength, solubility, and other known chemical characteristics as reported in several other publications Pfizer has admitted are prior art. Schmidt discloses that aryl sulphonic acids, such as benzene sulphonic acids, considerably increase the solubility of pharmaceuticals containing one or more basically reacting nitrogen atoms. 612 patent col.2 ll.14-41. Spiegel specifically identifies besylate as the preferred pharmaceutically-acceptable acid addition salt form of a pharmaceutical compound. 637 patent col.2 ll.38-39. Other patents not before the examiner during prosecution of the 303 patent also point to benzene sulphonate. U.S. Patent 3,970,662 to Carabateas (1976) ("Carabateas") discloses an intermediate dihydropyridine compound useful in the form of an acid addition salt derived from benzene sulphonate. 662 patent col.3 ll.35-49 & col.4 ll.20-24. U.S. Patent 4,432,987 to Barth (1984) ("Barth"), assigned to Pfizer, discloses the besylate acid addition salt form of a pharmaceutical composition having excellent pharmacokinetic properties, near-optimal solubility, and improved stability. 987 patent col.2 ll.45-46. Taken together, these references provide ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate.

The district court ignored the significance of these other prior art references suggesting the besylate salt because the pharmaceuticals disclosed in those prior art references were not described as useful to treat hypertension or angina, as is amlodipine. By not considering these references in its obviousness analysis, however, the district court clearly erred. As here, the besylate acid addition salt form was described in these prior art references as useful in promoting stability and solubility, as well as improving other physicochemical characteristics. That none of these references discloses a medication for treating hypertension or angina like amlodipine is therefore unimportant, if not actually irrelevant. As Pfizer concedes, the besylate part of the acid addition salt has no therapeutic effect, but merely serves as a means to deliver the amlodipine part of the

molecule to the body. Prior art disclosing the use of benzene sulphonate for improving the bioavailability of other pharmaceuticals-especially a dihydropyridine as disclosed by Carabateas-is therefore highly relevant in weighing the factors relating to obviousness.

Considering all of the evidence, we hold that a reasonable fact-finder could only conclude that Apotex indeed produced clear and convincing evidence that one skilled in the art, facing the problems including the stickiness of the tablet form of the maleate acid addition salt, would have been motivated to combine the teachings of the 909 patent, Berge, and other prior art, to produce the besylate salt of amlodipine.

Reasonable Expectation of Success

As noted above, the district court found that the skilled artisan would have had no expectation of success in making a besylate salt of amlodipine because there was no reliable way to predict the influence of a particular salt species on the active part of the compound. We cannot reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be. The problem with the district court's ultimate conclusion of non-obviousness based on that factual finding, however, is that case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. *See In re Corkill,* 771 F.2d 1496, 1500 (Fed.Cir.1985) ("Although [the inventor] declared that it cannot be predicted how any candidate will work in a detergent composition, but that it must be tested, this does not overcome [the prior art's] teaching that hydrated zeolites will work."); *see also Brown & Williamson Tobacco Corp. v. Philip Morris Inc.,* 229 F.3d 1120, 1125 (Fed.Cir.2000); *Merck & Co., Inc. v. Biocraft Labs., Inc.,* 874 F.2d 804, 809 (Fed.Cir.1989); *In re Merck* & Co., *Inc.*,

800 F.2d 1091, 1097 (Fed.Cir.1986). Indeed, a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt-including those specifically listed in the 909 patent itself-would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute. *Merck,* 874 F.2d at 809; *In re O'Farrell,* 853 F.2d 894, 903 (Fed.Cir.1988).

The evidence would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that an acid addition salt of besylate would form and would work for its intended purpose. *See In re Rinehart,* 531 F.2d 1048, 1053-54 (C.C.P.A.1976). Specifically, the evidence clearly shows that as soon as tablet processing problems arose with the amlodipine maleate tablet formulations, Dr. Wells readily compiled a list of seven alternative anions-including the besylate-each of which he expected would form an amlodipine acid addition salt:

> Q. And one of the reasons why you chose these various salts [sic], or suggested these various salts [sic], is because you expected that they would be able to make a salt of them, correct?
>
> A. There was an expectation, but that wasn't guaranteed.

But, once again, only a reasonable expectation of success, not a guarantee, is needed. *O'Farrell,* 853 F.2d at 903; *Brown & Williamson,* 229 F.3d at 1125. That reasonable expectation of success is further amply reflected in Dr. Wells' further testimony that he expected these seven amlodipine acid addition salts would show improved physicochemical characteristics over the maleate salt, including improved stability and non-stickiness:

> Q. And when you chose these salts ... you believed that if you could, in fact, make an amlodipine salt out of them, these might be a cure for the problems you were having with maleate, correct?
>
> A. Indeed.

We also note that the 909 patent placed no limitations on the acid addition salt whatsoever, except that it be non-toxic and formed from an acid containing a pharmaceutically-acceptable anion. Accordingly, the 909 patent contained a strong suggestion that any and all pharmaceutically-acceptable anions would form non-toxic acid addition salts and would work for their intended purpose-that is, to improve bioavailability of the active ingredient amlodipine and to improve handling and storage of amlodipine. Indeed, in proceedings before this court in *Pfizer v. Dr. Reddy's Laboratories* involving the 909 patent, Pfizer downplayed any difference between amlodipine maleate and any other acid addition salt form of amlodipine, including the besylate, prompting this court to observe that the sole active ingredient is amlodipine, and that it acts the same in the human body whether administered as a besylate salt or as a maleate salt. 359 F.3d at 1366.

Finally, there is a suggestion in Pfizer's supplemental filing with the FDA that it was known that the besylate salt of amlodipine would work for its intended purpose: "We feel that the change in salt form [from maleate to besylate] is justified since benzenesulfonate is a commercially acceptable salt, as exemplified by the tranquilizer mesoridazine (Serentil)." Thus, although Dr. Wells testified that it was not guaranteed whether amlodipine besylate would form and what its salient characteristics would be, "this does not overcome [the prior art's] teaching that [amlodipine besylate] will work." *Corkill*, 771 F.2d at 1500.

Considering all of the evidence, we conclude that the district court clearly erred in finding that Apotex failed to produce clear and convincing evidence that one skilled in the art would have had a reasonable expectation of success with the besylate salt of amlodipine.

"Obvious-to-Try"

To be sure, "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed.Cir.2006) (internal quotations omitted). Pfizer argues that, if anything, amlodipine in its besylate salt form would at most be "obvious to try," i.e., to vary all parameters or try each of numerous possible choices to see if a successful result was obtained. *O'Farrell*, 853 F.2d at 903.

Parties before this court often complain that holdings of obviousness were based on the impermissible "obvious to try" standard, and this court has accordingly struggled to strike a balance between the seemingly conflicting truisms that, under 35 U.S.C. § 103, "obvious to try" is not the proper standard by which to evaluate obviousness, *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A.1977), but that, under *O'Farrell* and other precedent, absolute predictability of success is not required. 853 F.2d at 903. Reconciling the two is particularly germane to a situation where, as here, a formulation must be tested by routine procedures to verify its expected properties. The question becomes then, when the skilled artisan must test, how far does that need for testing go toward supporting a conclusion of non-obviousness?

As we have said before, "[e]very case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts." *In re Jones,* 958 F.2d 347, 350 (Fed.Cir.1992). Consequently, courts cannot decide the obviousness or non-obviousness of a patent claim by proxy. Undue dependence on mechanical application of a few maxims of law, such as "obvious to try," that have no bearing on the facts certainly invites error as decisions on obviousness must be narrowly tailored to the facts of each individual case. As we stated in *DyStar,*

> Obviousness is a complicated subject requiring sophisticated analysis, and no single case lays out all facets of the legal test. [There is] danger inherent in focusing on isolated dicta rather than gleaning the law of a particular area from careful reading of the full text of a group of related precedents for all they say that is dispositive and for what they hold. When parties ... do not engage in such careful, candid, and complete legal analysis, much confusion about the law arises and, through time, can be compounded.

464 F.3d at 1367. On the facts of this case, however, we are satisfied that clear and convincing evidence shows that it would have been not merely obvious to try benzene sulphonate, but would have been indeed obvious to make amlodipine besylate.

First, this is not the case where there are "numerous parameters" to try. Rather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt. Although we recognize some degree of unpredictability of salt formation, *see, e.g., Sanofi-Synthelabo v. Apotex, Inc.,* 470 F.3d 1368, 1379 (Fed.Cir.2006), the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious. This is especially true here, where (1) as noted above, the skilled artisan had a reasonable (although not guaranteed) expectation that amlodipine besylate would form; (2) Pfizer conceded in

prior litigation that the type of salt had no effect on the therapeutic effect of the active ingredient, amlodipine, and was practically interchangeable, *Pfizer v. Dr. Reddy's Labs.*, 359 F.3d at 1365-66; and (3) numerous other publications (described above) clearly directed the skilled artisan to a pharmaceutically-acceptable acid addition salt made from benzene sulphonate, including, significantly, the Carabateas patent which taught the besylate acid addition salt form of another dihydropyridine pharmaceutical compound.

Second, this is not the case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell,* 853 F.2d at 903; *Medichem,* 437 F.3d at 1167. Here, as admitted by Mr. Davison, in selecting an acid addition salt formulation, one skilled in the art looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry. Berge clearly pointed the skilled artisan to 53 anions that, as of 1974, were pharmaceutically acceptable. As Dr. Wells' testimony and the Carabateas patent demonstrated, one of ordinary skill in the art was capable of further narrowing that list of 53 anions to a much smaller group, including benzene sulphonate, with a reasonable expectation of success.

Finally, Pfizer protests that a conclusion that amlodipine besylate would have been obvious disregards its "discovery" because it was obtained through the use of trial and error procedures. While the pharmaceutical industry may be particularly adversely impacted by application of an "obvious to try" analysis, *see, e.g., In re Merck,* 800 F.2d at 1100 (Baldwin, J., dissenting), that Pfizer had to verify through testing the expected traits of each acid addition salt is of no consequence because it does not compel a conclusion of non-obviousness here. In coming to this conclusion, we have not ignored the fact that "[p]atentability shall not be negatived by the manner in which the invention was made."

35 U.S.C. § 103(a). Nor are we ignorant of the fact that reference to "routine testing" or "routine experimentation" is disfavored. *See, e.g., In re Yates,* 663 F.2d 1054, 1056 n. 4 (C.C.P.A.1981) ("The Solicitor ... argues that it is 'not unobvious to discover optimum or workable ranges by routine experimentation.' In many instances, this may be true. The problem, however, with such 'rules of patentability' (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue-obviousness-and exalt the formal exercise of squeezing new factual situations into preestablished pigeonholes. Additionally, the emphasis upon routine experimentation is contrary to the last sentence of section 103.") (internal citation omitted); *In re Saether,* 492 F.2d 849, 854 (C.C.P.A.1974) ("In his argument that 'mere routine experimentation' was involved in determining the optimized set of characteristics, the solicitor overlooks the last sentence of 35 U.S.C. § 103.... Here we are concerned with the question of whether the claimed invention would have been obvious at the time it was made to a person having ordinary skill in the art-not how it was achieved.") (internal citation omitted); *In re Fay,* 52 C.C.P.A. 1483, 347 F.2d 597, 602 (C.C.P.A.1965) ("[W]e do not agree that 'routine experimentation' negatives patentability. The last sentence of section 103 states that 'patentability shall not be negatived by the manner in which the invention was made.' To support the board's decision that 'routine experimentation within the teachings of the art' will defeat patentability requires a primary determination of whether or not appellants' experimentation comes within the teachings of the art. Whether the subsequent experimentation is termed 'routine' or not is of no consequence.").

However, on the *particularized facts of this case,* consideration of the "routine testing" performed by Pfizer is appropriate because the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing. *Merck,* 874 F.2d at 809. The evidence shows that, upon

making a new acid addition salt, it was routine in the art to verify the expected physicochemical characteristics of each salt, including solubility, pH, stability, hygroscopicity, and stickiness, and Pfizer's scientists used standard techniques to do so. These type of experiments used by Pfizer's scientists to *verify* the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to *discover* a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success. This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably "routine" to one of ordinary skill in the art. Rather, our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation. *Cf. Velander v. Garner,* 348 F.3d 1359, 1368 (Fed.Cir.2003) (that one skilled in the art would view variability in producing fibrinogen in transgenic mammals as evidence that "expense, time and effort" would be involved did not equate to a conclusion that success was unlikely). Simply put, to conclude that amlodipine besylate would have been obvious, "the prior art, common knowledge, or the nature of the problem, viewed through the eyes of an ordinary artisan" merely had to suggest reacting amlodipine base with benzene sulphonic acid to form the besylate acid addition salt, and that that acid addition salt form would work for its intended purpose. *DyStar,* 464 F.3d at 1361. They did. *See O'Farrell,* 853 F.2d at 904.

We find this case analogous to the optimization of a range or other variable within the claims that flows from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson,* 315 F.3d 1325, 1330 (Fed.Cir.2003) (determining where in a disclosed set of percentage ranges the optimum combination of percentages lies is prima facie obvious). In *In re Aller,* 42 C.C.P.A. 824, 220 F.2d 454, 456 (1955), our predecessor court set forth the

rule that the discovery of an optimum value of a variable in a known process is usually obvious. *See also In re Boesch,* 617 F.2d 272, 276 (C.C.P.A.1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art."). Similarly, we hold that the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt. *Cf. In re Geisler,* 116 F.3d 1465, 1470 (Fed.Cir.1997) (" '[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.' " (quoting *Aller,* 220 F.2d at 456)); *In re Kulling,* 897 F.2d 1147, 1149 (Fed.Cir.1990) (finding no clear error in Board of Patent Appeals and Interferences' conclusion that the amount of eluent to be used in a washing sequence was a matter of routine optimization known in the pertinent prior art and therefore obvious). Indeed, the logical line of testing was to react benzene sulphonate with amlodipine to confirm the presence of a salt, and then to verify that the physicochemical properties of amlodipine besylate were adequate, particularly the trait of sufficient non-stickiness. The experimentation needed, then, to arrive at the subject matter claimed in the 303 patent was "nothing more than routine" application of a well-known problem-solving strategy, *Merck,* 874 F.2d at 809, and we conclude, "the work of a skilled [artisan], not of an inventor." *DyStar,* 464 F.3d at 1371; *see also In re Luck,* 476 F.2d 650, 652-53 (C.C.P.A.1973) (use of routine testing to identify optimum amounts of silane to be employed in a lamp coating, without establishing a critical upper limit or demonstrating any unexpected result, lies within the ambit of the ordinary skill in the art); *In re Esterhoy,* 58 C.C.P.A. 1116, 440 F.2d 1386, 1389 (1971) ("One skilled in the art would thus manifestly operate the Switzer et al. process under conditions most desirable for maximum and efficient concentration of the acid. The conditions recited in the claims appear to us to be only optimum and easily ascertained by routine

experimentation."); *In re Swentzel,* 42 C.C.P.A. 757, 219 F.2d 216, 219 (1955) ("It may well be that the size represents the largest particles suitable for appellant's purpose, but the determination of that desired size under the present circumstances involves nothing more than routine experimentation and exercise of the judgment of one skilled in the art."); *In re Swain,* 33 C.C.P.A. 1266, 156 F.2d 246, 247-48 (1946) ("In the absence of a proper showing of an unexpected and superior result over the disclosure of the prior art, no invention is involved in a result obtained by experimentation.").

Thus, while patentability of an invention is not negated by the manner in which it was made, "the converse is equally true: patentability is not imparted where 'the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success.' " *Merck*, 874 F.2d at 809 (quoting *In re Dow Chem. Co.,* 837 F.2d 469, 473 (Fed.Cir.1988)). For these reasons, we hold that Apotex introduced clear and convincing evidence that a skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine at the time the invention was made. Accordingly, we agree with the district court that a prima facie case of obviousness was established with regard to the claims of the 303 patent, albeit for different reasons.

Secondary Considerations

Before we turn to the remaining conflict between the parties-the district court's consideration of the objective indicia of non-obviousness-we must first address the district court's reference in its bench opinion to Pfizer's business decision to switch its commercial product from an amlodipine maleate formulation to an amlodipine besylate formulation, apparently as evidence of non-obviousness. *See Bench Order Tr.* at 6:21-7:1 ("Pfizer is a big company,

which by this time had a large investment in amlodipine maleate.... A decision to switch to some other product, or even to abandon the entire product, is the corporate equivalent of turning the Queen Mary."); *Bench Order Tr.* at 18:17-21 ("Pfizer would not have changed from the maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason."). The district court's reliance on this "objective consideration" seems suspect as there is no evidence in the appellate record to support the implicit finding that Pfizer ever considered abandoning amlodipine or stood to lose significant time and investment dollars. Indeed, we are not ignorant of the fact that pharmaceutical companies are in the business of research and development. We therefore disregard the district court's findings on this point as clearly erroneous, or in any event insufficiently probative of non-obviousness to overcome the evidence of the prior art teachings.

Evidence of unexpected results can be used to rebut a prima facie case of obviousness. *Peterson,* 315 F.3d at 1330. The district court found that, while amlodipine besylate was not superior to amlodipine maleate in every category of physicochemical properties, it nonetheless "clearly and unexpectedly illustrates a superior combination of properties when compared to" amlodipine maleate.[6] With regard to solubility, the 303 patent discloses that amlodipine besylate has a solubility of 4.6 mg/ml at pH 6.6, whereas amlodipine maleate has a solubility of 4.5 mg/ml at pH 4.8. The district court stated that any product having a solubility greater than 1.0 mg/ml is acceptable, and that "[t]he rest is sound and fury." *Bench Order Tr.* at 11:10. We conclude from this

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[6] We reject Apotex's assertion that the district court erred by giving weight to the commercial success of Norvasc® . The district court relied on the production of billions of amlodipine besylate tablets by Pfizer as evidence of non-stickiness rather than commercial success. Apotex's arguments with regard to an alleged absence of a "nexus" between the claimed features and the sales of Norvasc® are therefore irrelevant.

statement that the district court did not find that the solubility of amlodipine besylate was materially superior, much less "unexpectedly superior" to the solubility of amlodipine maleate. Similarly, we also conclude that the district court did not rely on non-hygroscopicity as a secondary consideration. Thus, the two allegedly unexpected and superior properties remaining are drug stability and tablet processing.

With respect to stability, the district court found that the 303 patent provided an ordinal listing of several tested salts descending in rank order from the most stable to the least stable, where the besylate salt was the most stable of the eight salts tested, and the maleate salt was the sixth most stable salt. The district court also found that amlodipine besylate was "sufficiently nonsticky to obtain commercial processability." Pfizer asserts that these improvements have significant practical value and are indicative of non-obviousness.

In contrast, Apotex asserts that the district court committed several errors when assessing secondary considerations. Specifically, Apotex asserts that the district court erred by comparing amlodipine besylate only to the maleate preferred embodiment disclosed in the 909 patent rather than the entire genus of amlodipine salts claimed therein. Apotex also asks this court to discount Pfizer's evidence of unexpectedly superior properties because the stability and drug processing properties of amlodipine besylate are neither "unexpected" nor "surprising." Finally, Apotex asserts that even if amlodipine besylate exhibits a better combination of solubility, pH, stability, non-hygroscopicity, and non-stickiness properties than other members of the genus of amlodipine salts, this purported superiority of amlodipine besylate is not significant enough as a matter of law to make it non-obvious. Apotex argues that amlodipine is the active ingredient and the sole source of therapeutic effects of amlodipine besylate, whereas the besylate is merely a means of delivering the amlodipine part

of the molecule. Thus, Apotex asserts, any salt need only exhibit *adequate* physicochemical characteristics in order to serve its purpose of delivering the amlodipine. Apotex contends that the record here demonstrates that the amlodipine maleate tablet also performs these same functions. The issue before us is whether, based upon the evidence as a whole, Pfizer's showing of superior results was sufficiently unexpected so as to rebut Apotex's showing of a prima facie case of obviousness.

While we agree that the teaching of a prior art patent is not limited to its preferred embodiment, *see Merck,* 874 F.2d at 807 ("the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered"), the other amlodipine salts of which Apotex complains (i.e., amlodipine tosylate and amlodipine mesylate) were not expressly recited in the 909 patent or elsewhere in the prior art. Thus, the district court's obligation to consider the entire range of prior art compounds would have been satisfied here by its comparison of the closest prior art compound to amlodipine besylate. *Kao Corp. v. Unilever United States, Inc.,* 441 F.3d 963, 970 (Fed.Cir.2006) (" '[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.' ") (quoting *In re Baxter Travenol Labs.,* 952 F.2d 388, 392 (Fed.Cir.1991)). However, there is precious little (if any) evidence to support any implicit finding by the district court that amlodipine maleate is actually the closest prior art compound to amlodipine besylate. Indeed, the prior art of Schmidt, Spiegel, Carabateas, and Barth, discussed above, evidences that one skilled in the art would expect an acid addition salt made from benzene sulphonate to have good physicochemical properties.

Another defect in the district court's reasoning is its failure to recognize that by definition, any superior property must be *unexpected* to be considered as evidence of non-

obviousness. *In re Chupp,* 816 F.2d 643, 646 (Fed.Cir.1987). Thus, in order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected. *Merck,* 874 F.2d at 808. Here, Pfizer's evidence must fail because the record is devoid of *any* evidence of what the skilled artisan would have expected. We will not simply presume that the skilled artisan would have expected that amlodipine besylate would have the same characteristics as amlodipine maleate, because as Pfizer asserts, its properties are not absolutely predictable. Further, Dr. Wells' testimony reflects the fact that he believed that amlodipine besylate would solve the problems of amlodipine maleate. Unrebutted testimony from Apotex's expert evidences that, given the range of 53 anions disclosed by Berge, one skilled in the art would expect those anions to provide salts having a range of properties, some of which would be superior, and some of which would be inferior, to amlodipine maleate. Pfizer has simply failed to prove that the results are unexpected. *Boesch,* 617 F.2d at 278.

Finally, we do not see the trial court's finding that amlodipine besylate had *adequate* physicochemical characteristics as sufficient to uphold the court's ultimate holding of unexpected superiority. Pfizer rejected amlodipine maleate not because it failed to exhibit an adequate combination of solubility, pH, stability in capsule form, and non-hygroscopicity, but because it could not be easily manufactured because of stickiness and limited stability of amlodipine maleate in the preferred commercial form of a tablet. The district court wrongly relied on the fact that the "besylate salt works" because considerable evidence shows that amlodipine maleate also worked for its intended purpose and even did so in human clinical trials, even though somewhat inferior in ease of tableting and projected shelf-life. At most, then, Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine. Creating a "product or

process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient ... to enhance commercial opportunities ... is universal-and even common-sensical." *DyStar*, 464 F.3d at 1368. Amlodipine besylate is obvious on the facts of this case because the 909 patent suggested-and Dr. Wells expected-that every other potential salt form of amlodipine would be adequate for its intended purpose, i.e., to increase bioavailability of amlodipine, and would solve the stickiness problem of the maleate salt. The fact that amlodipine besylate was the best of the seven acid addition salts *actually tested* proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art. *See Aller*, 220 F.2d at 456 ("[E]ven though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art."). These facts lead us to conclude that the resulting commercial embodiment claimed in the 303 patent, amlodipine besylate, does not satisfy the standards of patentability.

Alternatively, we hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed.Cir.1988). Here, the record establishes such a strong case of obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient. *Id.* at 769.

From our de novo assessment of the determination below on obviousness in view of all of the evidence and for the reasons articulated above, we conclude that the district court erred in holding that the claims of the 303 patent would not have been obvious.

III. CONCLUSION

Because we find claims 1-3 of the 303 patent invalid for obviousness, we find it unnecessary to address Apotex's assertion that Pfizer engaged in inequitable conduct during prosecution of the 303 patent and that its patent should therefore be declared unenforceable. For the aforementioned reasons, the district court's judgment is reversed.

REVERSED.

LINN, Circuit Judge, concurs in the result.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2006-1261

PFIZER, INC.,
Plaintiff-Appellee,

v.

APOTEX, INC. (formerly known as TorPharm, Inc.)
Defendant-Appellant.

Before MICHEL, Chief Judge, NEWMAN, MAYER, LOURIE, RADER, SCHALL, BRYSON, GAJARSA, LINN, DYK, PROST, and MOORE, Circuit Judges.

ORDER

The Appellee, Pfizer, Inc. filed a combined petition for panel rehearing and rehearing en banc, and a response thereto was invited by the court and filed by the Appellant, Apotex, Inc. The petition for rehearing was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response were referred to the circuit judges who are authorized to request a poll whether to rehear the appeal en banc. A poll was requested, taken, and failed.

Apotex, Inc. moves for expedited denial of rehearing and rehearing en banc, and for expedited issuance of the mandate. Pfizer, Inc. opposes.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The petition for rehearing and rehearing en banc is denied.

(2) The motion for expedited denial of rehearing and rehearing en banc is denied as moot.

(3) The motion for expedited issuance of the mandate is granted.

NEWMAN, LOURIE, and RADER, Circuit Judges, would rehear the appeal en banc.

NEWMAN, Circuit Judge, dissents in the denial of the petition for rehearing en banc in a separate opinion.

LOURIE, Circuit Judge, dissents in the denial of the petition for rehearing en banc in a separate opinion.

RADER, Circuit Judge, dissents in the denial of the petition for rehearing en banc in a separate opinion.

FOR THE COURT

May 21, 2007
Date

s/ Jan Horbaly
Jan Horbaly
Clerk

ISSUED AS A MANDATE : MAY 21, 2007

NEWMAN, Circuit Judge, dissenting from the denial of rehearing *en banc*.

The court has not accepted the suggestion that this case be reviewed *en banc*, and the panel was unpersuaded by the argument that the decision is incorrect when the law of precedent is applied. I write separately because the panel's statement of the applicable law and its application to the facts of this case are inconsistent with the court's precedent. Our obligation as an appellate court is to assure that the law is both correctly stated and correctly applied. When inconsistency is raised by the panel's treatment, our obligation is to assure that conflicts with precedent -- whether real or apparent -- are resolved, as well as to assure that the law is correctly applied. From the court's denial of rehearing *en banc*, I respectfully dissent.

The ruling in this case has important policy as well as legal implications, as the many amici curiae point out, each side stressing a different aspect of the effect on commercial activity in the pharmaceutical field. Both sides acknowledge that the effects of chemical changes on properties of medicinal products is not predictable; the difference residing in the panel's acceptance of the long-discredited "obvious to try" standard, on which the panel superimposes the theory that the skill of these inventors guided them to trial of the besylate salt (despite the prior art's preference for the maleate salt), thereby negating patentability. The panel's application of the obvious-to-try standard is in direct conflict with precedent; it has long been the law that "patentability shall not be negated by the manner in which the invention is made." 35 U.S.C. § 103. In *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990) this court stated that "we have consistently held that 'obvious to try' is not to be equated with obviousness." In *In re Tomlinson*, 363 F.2d 928, 931 (CCPA 1966) the court explained that "there is usually an element of 'obviousness to try' in any research endeavor, that . . . is not undertaken with complete blindness but rather with some semblance of a chance of success." The

amici curiae representing research pharmaceutical industries in this petition point out that methodical experimentation is fundamental to scientific advance, and particularly for biological and medicinal products, where small change can produce large differences. At the trial there was no contradiction to the testimony of Pfizer's expert witness Dr. Anderson that "one of ordinary skill in the art could neither draw any conclusions nor have any expectations about the properties of amlodipine besylate from the properties of a besylate salt of a different compound." Pfizer Br. at 7. Indeed, the parties stipulated this scientific fact.

Nor was there any evidence contradicting Pfizer's position that "the superior properties at issue were not some abstract concept of 'good' properties, but specific properties which solved both the sticking and instability problems of the prior art, while providing non-hygroscopicity and good solubility. . . . Trade-offs in salt properties are the rule, and one of skill must usually accept some undesirable properties to achieve other desirable ones. Amlodipine besylate, unlike any other amlodipine salt, presented no trade-offs." *Id.* The panel further erred in declining to give weight to these acknowledged "secondary considerations" of unexpected results. *See Richardson-Vicks, Inc. v. Upjohn Co.*,122 F.3d 1483 (Fed. Cir. 1997) (evidence of unexpected results must be considered); *Ruiz v. AB Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000) ("Our precedents clearly hold that secondary considerations, when present, must be considered in determining obviousness.")

The panel decision changes the criteria as well as the analysis of patentability, with results of particular significance for their effect on the conduct of R&D, the costs of drug development, and the balance between generic access to established products and the incentive to development of new products. The amici curiae on both sides of the issue stress different policy considerations: the pharmaceutical research companies point out that diminished access to patenting will affect the kind and direction of product

development; the generic producers point out that the sooner they can enter the market for established drugs, the lower the consumer price. The placement of the balance in this ever-present conflict between innovator and copier has long engaged the public and Congress, and needs must continue to do so. Meanwhile, however, it is inappropriate for a panel of this court to make a change in the precedent by which both sides of the debate have heretofore been bound.

Stability of precedent and the uniform application of correct law to achieve the correct result are the assignment of the Federal Circuit, for our rulings are of nation-wide effect. A primary purpose for which our court was formed was to provide the judicial stability that supports commercial investment -- this was a unique judicial role, and was adopted in recognition of the dependence of technology-based industry on an effective patent system. It was recognized that a nationally uniform, consistent, and correct patent law is an essential foundation of technological innovation, which is today the dominant contributor to the nation's economy. *See the Report of the Domestic Policy Review of Industrial Innovation*, Department of Commerce 1979 (stressing the need for judicial administration of correct and uniform patent law). In enacting the implementing statute, Congress explained:

> The purpose [of establishment of the Federal Circuit] is to resolve some of the myriad structural administrative and procedural problems that have impaired the ability of our Federal courts to deal with the vast range of controversies among our citizens and to respond promptly and meaningfully to their demands for justice . . . which include the inability of our present system to provide a prompt, definitive answer to legal questions of nationwide significance . . .

S. Comm. on the Judiciary, Federal Courts Improvement Act of 1981, S. Rep. No. 97-275, at 1 (1981).

When conflicts arise between panel decisions of the Federal Circuit the ensuing uncertainty is of national scope, contravening the purpose of establishing this court. This adds weight to our obligation to undertake *en banc* review, both to reestablish consistency in the law and to correct errors in panel decisions. In 1998, in a letter to the Commission on Structural Alternatives for the Federal Courts of Appeals, Justice Scalia wrote:

> [T]he function of en banc hearings . . . is not only to eliminate intra-circuit conflicts, but also to correct and deter panel opinions that are pretty clearly wrong . . . . The disproportionate segment of [the Supreme Court's] discretionary docket that is consistently devoted to reviewing [a regional court of appeals'] judgments, and to reversing them by lop-sided margins, suggests that this error-reduction function is not being performed effectively.

Letter dated Aug. 21, 1998, *Hearing before the S. Subcomm. on Administrative Oversight and the Courts of the S. Comm. on the Judiciary*, 106th Cong. 72 (1999).

Justice O'Connor wrote in similar vein:

> It is important to the federal system as a whole that the Courts of Appeals utilize en banc review to correct panel errors within the circuit that are likely to otherwise come before the Supreme Court.

Letter dated June 23, 1998, id. at 71.

For the Federal Circuit, it was intended and expected that this court would provide uniform national law in all of the fields assigned to our exclusive jurisdiction; not only in patent law. Our cases are rarely factually simple, and when there arise apparently divergent panel statements of the law and its application, the responsibility for en banc review

looms large. The goal of judging is "full, equal and exact" enforcement of the law. *See* Roscoe Pound, "The Etiquette of Justice," 3 Proceedings Neb. St. Bar Assn. 231 (1909) ("full, equal and exact enforcement of substantive law is the end" of the judicial process). Through the system of en banc review, courts can remedy panel lapses, if indeed this decision represents such a lapse, or uniformly adopt panel advances in the law, if indeed this decision represents such an advance. From the court's decision to decline this review, I must, respectfully, dissent.

LOURIE, Circuit Judge, dissenting from the denial of rehearing en banc.

I respectfully dissent from the court's decision not to rehear this case en banc. At bottom, I consider that the decision of the panel was incorrect. But, we do not rehear appeals simply because a non-panel member disagrees with its result. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1043 (Fed. Cir. 2006) (Lourie, J., concurring) ("I do not believe that every error by a panel is enbancable. A panel is entitled to err without the full court descending upon it."). Federal Rule of Appellate Procedure 35(a) provides that "[a]n en banc hearing or rehearing is not favored and ordinarily will not be ordered unless: (1) en banc consideration is necessary to secure or maintain uniformity of the court's decisions; or (2) the proceeding involves a question of exceptional importance." Our Internal Operating Procedures ("IOPs") state that "[a]mong the reasons for en banc actions are: (1) necessity of securing or maintaining uniformity of decision; (2) involvement of a question of exceptional importance; (3) necessity of overruling a prior holding of this or a predecessor court expressed in an opinion having precedential status; or (4) the initiation, continuation, or resolution of a conflict with another circuit." IOP 13(2).

However, consistent with those established criteria for taking a case en banc, I consider that the panel erred in its legal determinations, and that those errors will confuse the law relating to rebuttal of a prima facie case of obviousness of a chemical compound. Thus, an en banc hearing is warranted in this case in order to maintain uniformity of the court's decisions and because it presents questions of exceptional importance.

The panel reversed the district court's decision that claims relating to amlodipine besylate (the active ingredient in the hypertension drug Norvasc®) were valid and nonobvious after a bench trial. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). In my view, several legal

errors were made in this decision, and improper deference was given to fact-findings of the district court.

First, the panel failed to defer to fact-findings made by the district court that were not clearly erroneous regarding the unexpected properties of amlodipine besylate. Evidence in the record, including trial testimony of experts and Pfizer scientists, internal research and development documents, and a scientific article, supported the district court's finding that "the besylate salt clearly and unexpectedly exhibited a superior combination of properties when compared to what was suggested in the preferred preparation." *District Court Oral Op. Tr.* at 23:13-15; *see* Pet. for Reh'g en banc at 5-6. The panel disregarded that express finding of fact, holding that "Pfizer has simply failed to prove that the results are unexpected." *Pfizer*, 480 F.3d at 1371. Moreover, relying on the testimony of both parties' experts, the district court found that there was no reasonable expectation of success with regard to using the besylate salt form of amlodipine. *District Court Oral Op. Tr.* at 23:1-9. However, rather than give deference to the district court's fact-findings, the panel substituted its own finding that a reasonable expectation of success existed in the art. *See Pfizer*, 480 F.3d at 1361, 1364-65 ("The record also satisfies us that, contrary to the district court's finding, a reasonable fact-finder could only conclude that the skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine."). Much public discussion has occurred, and even judicial comments in opinions, that we should defer to district court judges concerning certain aspects of claim construction, which we have held is a matter of law. Be that as it may, it is undisputed that we must defer to fact-findings by a district court, unless they are clearly erroneous, and I do not believe that they were here.

In addition, the panel improperly placed greater importance on the therapeutic value of a claimed compound over the value of its physical properties. The panel concluded that the improvement of the invention, which related to drug

formulation, viz., increased stability and decreased stickiness, was "insufficient" to meet the standards of patentability. *Id.* at 1368 (emphases added) ("[W]e hold that the *optimization of the acid addition salt formulation* for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation *has no effect on the therapeutic effectiveness* of the active ingredient and the prior art heavily suggests the particular anion used to form the salt."). I read that conclusion as improperly requiring a compound to possess a specific type of improvement over the prior art—in this case, improved therapeutic properties—to be patentable, negating other important properties, a conclusion that is not compelled by our case law and not sound. Any useful and unexpected property should be eligible to overcome a prima facie obviousness determination. *See In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. . . . There is no basis in law for ignoring any property in making such a comparison.").

Third, the panel also found that the invention was the result of routine experimentation, and therefore was not patentable. *See Pfizer*, 480 F.3d at 1367 (emphases added) (stating that the "type of experiments used by Pfizer's scientists to *verify* the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to *discover* a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success"). That conclusion conflicts with the statutory requirement that "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103(a). Moreover, the conclusion contradicts the district court's supported findings that the results were unexpected, and that the experiments led to showing the totality of the properties of the invention, *see Papesch*, 315 F.2d 381, which makes the compound nonobvious, not merely to the *verification* of results.

In addition, holding an inventor's expectations of success against the objective unexpectedness of the properties of the compound unfairly suggests that an inventor should try only that which he doubts will work. *See Pfizer*, 480 F.3d at 1371 ("Dr. Wells' testimony reflects the fact that he believed that amlodipine besylate would solve the problems of amlodipine maleate."). Inventors generally are optimistic about what they choose to experiment with, but that does not necessarily suggest obviousness.

These issues are of exceptional importance. Chemical and pharmaceutical compounds often can be found to be prima facie obvious, as they are based on prior work that could reasonably suggest them, *see KSR Int'l Co. v. Teleflex Inc.*, --- S.Ct. ---, 2007 WL 1237837 (Apr. 30, 2007), but commercialization of such compounds may depend on their possession of unexpected properties. Such properties may be biological or physical. A failure to recognize all such properties that may be relevant to the value of such a compound may doom the compound to being poured down the drain rather than becoming an important therapeutic. The general public, innovative companies, and, ultimately, generic companies, depend upon faithful adherence to this principle. In addition, our cases hold that unexpected properties make for non-obviousness, *see Papesch*, 315 F.2d 381, and this decision disdains such properties if they are not biological. That is a conflict with our precedent that needs resolution.

Not least, the question of deference to district courts, at least on fact issues, needs reaffirming. We must not shy away from reversing fact-findings that truly are clearly erroneous, as we do encounter them from time to time, but this case does not present them.

Thus, I would rehear this case, and I dissent from the court's determination not to do so.

RADER, Circuit Judge, dissenting from the denial of rehearing *en banc*.

I respectfully dissent from the decision to deny rehearing.

In this case, the trial court made the factual determination that the besylate salt form of amlodipine had unexpected superior properties over the closest prior art. Accordingly, the underlying patent ('303) was valid and nonobvious. Three separate district courts held trials involving the '303 patent. Indeed, each of those three different district court judges came to the same factual conclusion regarding the nonobviousness of amlodipine besylate. Because the factual determinations in the case below were not clearly erroneous, this court should have deferred to the district court's factual findings.

As the testimony indicated, the properties of new pharmaceutical salt forms are entirely unpredictable. Even the Berge reference on which the panel relied clearly states: "Unfortunately there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." The district court agreed and made the factual determination that the superior properties of amlodipine besylate over the prior art (increased stability and decreased stickiness) were indeed unexpected – a finding that deserved deference.

Furthermore 'obvious to try' jurisprudence has a very limited application in cases of this nature. With unpredictable pharmaceutical inventions, this court more wisely employs a reasonable expectation of success analysis. In this case, salt selection is unpredictable, thus rebutting, as most other courts found, any reasonable expectation of success. Although the panel gives "lip service" to the principle that 'obvious to try' does not work in this field, it nonetheless appears to be the basis for its decision in this case. In addition, the panel discerned a reasonable expectation of success by giving

undue emphasis to the inventor's subjective hopes for the outcome of his experiments.

The panel also mistakenly determined that the superior properties of the besylate did not overcome a prima facie case of obviousness because they showed no superior therapeutic value—the maleate salt form of amlodipine worked just as well as the besylate form in clinical trials. Therapeutic value, however, is just one property of a pharmaceutical. Other properties, such as solubility, stability, hygroscopicity, and processability, must also play a role in the analysis of advantages. The superior properties of the besylate salt form of amlodipine, overcame the stability and stickiness problems that existed with the maleate salt form and created a superior formulation. Although the maleate salt form was also therapeutically effective, the besylate form was still a significant improvement because it overcame the stability and processing problems that could have prevented successful commercial marketing.

The panel also found that amlodipine besylate was not patentable since it was made by a routine testing or a "well known problem solving strategy." This clearly violates the statutory mandate that "patentability shall not be negatived by manner in which the invention was made." 35 U.S.C. § 103(a). Many if not most pharmaceutical inventions are discovered through a routine screening protocol or through an established trial and error process. Pharmaceutical inventions discovered by these routine screening methods include not only new formulations and salt forms, but also include the active pharmaceutical compounds themselves. Thus, this decision calls into question countless pharmaceutical patents, which in turn could have a profoundly negative effect on investments into the design and development of new life-saving pharmaceuticals. With many questions about this case, I would have reheard it en banc.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS

3-C-5289 (JMR/MTM)

PFIZER, INCORPORATED,
Plaintiff,

-v-

APOTEX, INCORPORATED
Defendant.

BENCH ORDER: January 17, 2006

BEFORE CHIEF JUDGE JAMES M. ROSENBAUM (Of the District of Minnesota) Chicago, Illinois

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In the matter of Pfizer, Incorporated versus Apotex, Incorporated, this is an action for patent infringement under the Hatch-Waxman Act, at 21 U.S.C. Section 355 J, and 35 U.S.C. Section 271(e)(2). Congress apparently enacted Hatch-Waxman to expedite the delivery of pharmaceuticals to the consuming public. Plaintiff, Pfizer, Incorporated, makes, and it holds a patent on a commercial drug product called Norvasc, an extremely successful drug. The drug is primarily used to treat high blood pressure angina. Norvasc is covered by two patents, number 4,572,909, that's the '909 patent, and 4,872,303, the '303 patent. Defendant, Apotex, Incorporated, has filed an Abbreviated New Drug Application, indicating its intent to produce a generic drug product which will be the chemical equivalent to the invention claimed in the '303 patent.

Pfizer asserts that the defendant's application is an act

of infringement and seeks an injunction barring Apotex from producing its product until the expiration of the protection afforded by the '303 patent. Apotex has replied by challenging the validity of the '303 patent. This challenge is the gravamen of this lawsuit.

The Court announces its decision pursuant to Rule 52 of the Federal Rules of Civil Procedure, which provides in part, that "in all actions tried upon the facts without a jury, the Court shall find the facts specifically and state separately its conclusions of law thereon. It will be sufficient if the findings of fact and conclusions of law are stated orally and recorded in open court following the close of the evidence." There are internal ellipses within that quote.

The Court begins by adopting and incorporating the parties' excellent stipulation of uncontested facts. Having done so, it will be apparent that there are very few contested facts in this case. The parties vigorously contest the upshot of many of the facts and events which have occurred here, but with very few exceptions they agree as to the actual occurrences.

Norvasc's active ingredient is amlodipine, a chemical compound isolated as a chemical base. Amlodipine is in fact the invention which is the subject of the '909 patent. It is frequently the case, then, in order to make a pharmaceutical drug from a chemical base, it is necessary to combine the base with a chemical acid to create a chemical salt. This very common event is also described in the '909 patent. An ideal pharmaceutical salt is stable, soluble, pure, and able to be processed in marketable dosage form.

Pfizer's '909 patent claimed not only the active amlodipine ingredient, but also a pharmaceutically acceptable acid addition salt containing amlodipine. Within its text, the patent alludes to no fewer than a dozen possible amlodipine salts. The '909 patent specifically identifies amlodipine maleate as the preferred salt form. Having identified --

having invented amlodipine and obtaining its patent, Pfizer undertook to develop it for commercial sale. The path proved rocky.

When it began to prepare amlodipine maleate for commercial distribution, two major problems developed. During testing, the maleate salt revealed, first, chemical instability; second, when Pfizer's product was being tested for production in the tablet form, a form all parties agree is the most desirable and the most desired by consumers, the blend of amlodipine maleate showed a tendency to stick or film on the tablet-making machinery. This made it difficult to produce a fast, economical tablet and seriously complicated the ability to mass produce reliable dosage amounts. The problems were so great, that even after isolating an efficacious product and protecting it by an issued patent, Pfizer seriously considered abandoning commercial development of the product. Pfizer had a drug which could help the public, but they couldn't get it to needful patients.

This was no small problem, as acknowledged by Apotex's expert, Dr. Michael Cima. Pfizer is a big company, which by this time had a large investment in amlodipine maleate. It was well on its way to commercial distribution. A decision to switch to some other product, or even to abandon the entire project, is the corporate equivalent of turning the Queen Mary.

Pfizer's research team in Sandwich, England, returned to their laboratory benches, seeking new salts which might possess the desired chemical stability and tablet-making properties. Pfizer employees, Dr. James Wells and Edward Davison, tested various salt forms for several properties: Solubility, stability, nonhygroscopicity, and processability or stickiness.

As is typical in chemical laboratory work, their lab notes were recorded in laboratory notebooks. Testimony revealed that Pfizer had a procedure under which it issues

these notebooks, apparently dated and numbered. They are kept and maintained by the company as research and business records.

Doctors Wells and Davison also described an informal, and today somewhat problematic, informal set of laboratory notebooks which they themselves adopted. These were not the Pfizer-issued books, but were apparently obtained and maintained in a less formal fashion by this team. These notebooks were apparently kept in laboratory drawers, identified by the researcher's initials, and dated.

Of interest in this case, it now appears some 20 years after the facts, that certain of these notebooks, including some of their original records of test results, have been lost.

The Court finds, first, that these notebooks did exist.

Their existence is independently confirmed by allusion to some of their recorded experiments in Pfizer's regularly issued and maintained laboratory notebooks. Here the Court makes an explicit finding: Apotex claims the absence of the internally maintained -- informally maintained laboratory notebooks is, de facto, spoliation. It claims the absence of these documents is a smoking gun, aimed at the heart of the research supporting the '303 patent. The Court rejects this position. The '303 patent was issued in 1987. The informal laboratory notebooks were necessarily authored and utilized prior to that time. Both Dr. Wells and Davison have long departed from Pfizer, and the amlodipine team has scattered to the winds. It is not at all inconceivable to the Court, that when these out-of-the-ordinary notebooks were found by some impossible to identify Pfizer employee, they were simply tossed. The patent was ages old, as patents go. Certainly it would be more desirable to have these documents, but two decades after the events, the Court cannot find their absence to be evidence of skullduggery. There is absolutely no evidence, beyond their absence, that

these unavailable notebooks contained any damaging or indeed supportive material for either side.

Turning away, then, from what even a color-blind judge considers a red herring, and back to the real issues at hand, the research team hit upon the use of benzene sulphonate as one of the acids which could produce an acceptable salt in combination with the amlodipine base.

This was no small task. As will be discussed below, many organic acids will not do so. Some will only form oils, some are unstable, some produce undesirable or dangerous byproducts. The addition of the benzene sulphonate turned amlodipine into a besylate salt. This was the Pfizer team's discovery, of which a good deal more later. But it is this compound, amlodipine besylate, which is the subject of the now-challenged patent. Pfizer applied for what is now the '303 patent. Cited as relevant references for the '303 patent was Pfizer's '909 patent, U.S. patent number, numbers 3,816,612, and 4,032,637, and a scholarly article, Pharmaceutical Salts, which will be referred to as the Berge Article, authored by Stephen Berge, et al. And that is in Pharmaceutical Salts, 66 Pharmaceutical Sciences 1, January 1977.

Pfizer claimed the amlodipine besylate displayed the most desirable set of properties to produce a commercial amlodipine product for market. These included good solubility, stability, nonhygroscopicity, and processability.

In specific, Table 1 of the '303 patent details solubility. It gives solubility values for amlodipine besylate, amlodipine maleate, and several other salts. The patent is clear: A salt with a solubility factor greater than 1.0 milligrams per milliliter is desirable. This solubility permits the production of a commercial product, which must be mixed with diluents, carriers, and pharmaceutically inactive products in order to make a dispensable tablet or injectable dosage. This solubility, in particular, allows sufficiently

large amounts of active ingredient, here amlodipine, to be given to the patient in a pill, which is convenient for administration. Greater solubilities aid in the formulation of parenterel, that is injected, dosage forms of the drug.

Table 1 lists aqueous solubility of amlodipine besylate at 4.6 and amlodipine maleate at 4.5. This figure was much challenged at trial, and may not be accurate.

Evidence was offered to suggest it was inaccurate, it was mistaken, it was faked, or it was accurate and varied from batch to batch, or experiment to experiment. It may even have been a figure mistakenly transposed from other results, mixed up with an analysis of saline solutions. Other uncontested evidence suggested it may have varied as a result of greater or lesser skill in manufacture or in varying purities of the amlodipine being analyzed. The Court considers there is good evidence showing that amlodipine besylate actually demonstrates a solubility of 3.5 milligrams per milliliter in an aqueous solution, at JTX 9, at 3, and 4.6 in a saline solution, PTX 90.

Notwithstanding Apotex's zealous urging, the Court does not find this challenged number, even if it is off slightly, to amount to a hill of beans. The question for a drug company seeking to produce a drug product for tablet and injection administration is whether the product has a solubility which exceeds 1.0 milligrams per milliliter. Amlodipine besylate does so. The rest is sound and fury, signifying nothing. Any misstatement there is, and the Court does not consider it so, is immaterial.

The '303 patent next ranks stability. It provides a table in column 3 of the patent listing several tested salts. This table shows the besylate salt to be the most stable of eight salts listed. The maleate salt is sixth on the list. This table is purely ordinal. It just orders the chemicals by stability, most stable to least, without giving solubility

values. It merely bears a set of arrows descending in a stability rank ordering.

The patent identifies hygroscopicity. The tendency of a salt to take on water as another issue. Here, the Court recognizes that a chemical can take on water in more than one way: It can simply attract water to its surface, water can be incorporated as part of its molecule or into its crystalline structure, in both predictable and unpredictable fashions. And water, when taken into or onto a molecule can either be inactive, or it can have that water enter into chemical reactions with the salt, which can be highly undesirable in pharmaceuticals.

Pharm -- Apotex's experts suggest that amlodipine besylate is actually hygroscopic, which renders its claim that it is not hygroscopic false. The Court rejects their testimony on this point. In the Court's view, their testimony is accurate only in the most hyper technical sense, and not as applied to the facts of this case. The base problem of the case, and the ultimate problem with amlodipine maleate, the subject of the '909 patent, is that along with its stickiness, it is subject to chemical changes when exposed to water. When exposed to water, it undergoes the Michael Addition reaction, creating at least ten degradation products, making it unsuitable for medical purposes.

Defendant's experts suggest that amlodipine besylate is hygroscopic for three reasons: First, apparently, because it precipitated from an aqueous solution, the product can exist as a hydrate; second, because it may have water within its crystalline structure; and third, because it can have water on its surface and at extended temperatures and humidities. All three of these facts are true. Each is entirely unenlightening. The reason is simple: Everyone recognizes that the major problem, indeed the dangerous problem, with the maleate salt, is its susceptibility to the Michael Addition reaction.

Amlodipine besylate does not manufacture -- manifest this dangerous and pharmaceutically disqualifying tendency. In this regard, and fairly considered, the Court finds that in the context of this case, Pfizer's patented product is not hygroscopic, and its patent claims to that effect are entirely true.

The '303 patent's final listed factor is processability, or stickiness. Pfizer measured for stickiness by running numbers of tablets and measuring the amount of product sticking in the punch face after each run. Obviously, a number of different techniques were used. The patent states that tablets were produced in runs of 50, 100, 150, 250, and 300 -- if I left out 200, that's fair too -- during the course of the testing. While no documentary evidence was produced which showed that those tests were conducted, evidence was certainly adduced based upon the work conducted by Ms. Teresa Cutt, showing extensive runs of tablets resulting in tens of thousands of tablets of amlodipine besylate. Here I reference JTX 10, Figure 8; PTX 86, Figure 10; PTX 88, and -- at Figure 1. Internal memos show testing after 150 tablets for all of the salts listed in the patent, JTX 9. There do not appear to be rigorous tests for stickiness in these cases, although it appears that the processing runs worked. These larger production runs were not cited in the '303 patent. Under any circumstance, however, the Court finds that extensive testing was done, and it was shown, first, that the amlodipine besylate was sufficiently nonsticky to obtain commercial processability, and whether or not there are exact documents supporting it, I do not find they are a false declaration in any sense.

So, I focus then on the ultimate question, and that is the validity of the '303 patent. I begin with the essential understanding of the burden which is borne by a party who wishes to invalidate an issued patent. The party which challenges a patent has the burden of showing invalidity by clear and convincing evidence. This burden, of course, is noted in countless cases, but for the purposesof this opinion, I

cite *Kaufman vs. Lantech* at 807 F.2d 970 at 973, Fed. Cir. 1986. And the reason for this burden is because in order to have a stable patent system, an issued patent enjoys a presumption of validity and regularity, unless the challenger shows substantial evidence that something was seriously wrong.

In this case, Apotex advances three theories to support its claim that Pfizer's '303 patent is invalid. They claim, first, the '909 patent anticipates the '303; second, the '303 patent is invalid for obviousness; and third, plaintiff engaged in inequitable conduct before the Patent Office. If Apotex is able to prove any of these theories by clear and convincing evidence, its challenge would be successful and the '303 patent would be found invalid. The Court determines as a matter of fact and law, that Apotex has failed to sustain its burden.

Directing its attention to anticipation, I note that 35 U.S.C. Section 102(a) provides that an invention must be novel to merit a patent. A patent is not novel if it is anticipated or described in a printed publication, in this or a foreign country. An invention is anticipated if every element or limitation found in the patent claims can be found in a single prior art reference. Here I refer to *Scripps Clinic & Research* at 927 F.2d 1565 at 1576, Fed. Cir. 1991. Apotex asks the Court to find the '909 patent anticipates the '303 patent.

The defendant argues that the '909 patent claims amlodipine and amlodipine mixed with one of a class of salts of which besylate is a member. According to Apotex, the '909 patent claims a limited genus of amlodipine salts of which amlodipine besylate is a species. From this assertion, they claim that the '909 patent anticipates the '303. In general, these areas are discussed and considered in *In re Petering* at 301 F.2d 676 at CCPA 1962; and *In re Schauman*, 572 F.2d 312, CCPA 1978. Apotex's reliance on these cases is misplaced.

The law has established that a claim to a species anticipates a genus, but a claim to a genus doesn't necessarily anticipate a species. *Eli Lilly*, and I cite here *Eli Lilly v. Barr Labs* at 251 F.3d 955 at 971, from the Fed. Cir. 2001. The '909 patent explicitly discloses one salt form of amlodipine as the preferred salt: the amlodipine maleate. The patent discloses other potential salt forms; indeed, it suggests at least a dozen. But the besylate salt is not included in the list. The '909 patent surely covers the besylate salt, but the Court finds as a matter of law that it does not disclose it.

A person of ordinary skill in the art looks in vain at the '909 patent to find anything other than amlodipine maleate to be the preferred product. The Court finds there is nothing in the '909 patent, let alone clear and convincing evidence, to show that it anticipates the '303 patent.

Defendants argue that the genus of pharmaceutically acceptable salts is small, thus a claim to the genus anticipates this finite species. They cite to the Berge article which was known at the time of the '909 patent, but the Berge article identifies more than 50 anions and lists the frequency of their use. Benzyl sulphonate is mentioned and noted to have been used .25 percent of the time. This is a mere one time in 400. It is scarcely to be suggested that this is a directive arrow pointed to by the '909 patent.

Apotex's argument is ultimately a linguistic and syllogistic argument. It goes as follows: First the '909 patent claims, quote, a pharmaceutical composition comprising an anti-ischaemic or anti-hypertensive amount of a compound according to claim 1, and a pharmaceutically acceptable diluent or carrier, that's JTX 40, and a pharmacologically accepted anion. Therefore, the '909 patent anticipates amlodipine besylate. The argument proves too much. There are, according to Berge, over 50 anions, which have historically been accepted by the FDA. That science will ultimately produce at least one more, and

probably many more, which will ultimately be accepted by the FDA, is a virtual certainty. If Apotex's argument is accepted, the '909 patent will anticipate products which have not yet been developed, but which may be later accepted at some later time by the FDA. This is not clear and convincing. Their anticipation arguments fail because the '909 patent discloses the genus and several specific salts, it does not disclose the benzene sulphonate, a species of the '909 genus. The patent is not anticipated.

I also refer to the fact that there is an allusion to the fact that the -- I should also note, that the evidence indicated the only prior uses of a besylate salt, for pharmaceutical purposes, was in a tranquilizer, and a veterinarian product, each of which is entirely unrelated to the product in question here. It does not appear that it has ever been used in any fashion for anything relating, ah, to a hypertensive or angina protecting preparation. There was a reference also, however, to the fact that in 1992 -- 1982 -- there was an experiment in which a sulphonate was used and obtained a salt. I recognize, however, that this was an experiment conducted by one Burges, referred to in Exhibit 21, but the product involved was methane sulphonate, and this scarcely, once again, directs a particular, ah, person, and I will focus further in a moment on the person, to produce a besylate salt. I note that the actual exhibit said that they "managed to form." Managing to form does not suggest anything along the line that this is pharmaceutically acceptable and will ultimately be a pharmaceutically acceptable process, or contain the necessary attributes.

I now focus on the fact that Apotex has advanced an estoppel argument. In doing so, they seize on typed words which Pfizer has submitted to the Patent Office and to the U.S. Court of Appeals for the Federal Circuit. In certain statements to that office and the Circuit, Pfizer stated that the '909 patent covers amlodipine besylate, for purposes of extending the '909 patent and in an action of infringement -- or for infringement of that patent. It is now Apotex's

argument that these statements are antithetical to Pfizer's claim that the '303 patent is for something new and shows somehow its acquiescence in Apotex's claim that the '909 patent anticipates and makes obvious the '303 patent. Remarkably, the Court notes that Harris Pitlick, Apotex's patent law expert, neither talked about nor did he offer any opinion on this theory. This is probably for the best, because as I've indicated, unlike, ah -- this is probably for the best, because unlike a truly hygroscopic salt, this theory does not hold water. The Court cannot gainsay the possibility that Apotex feels it does not need expertise on the subject, but the Court finds the argument weak in the extreme.

The Court is well satisfied that Pfizer's declarations are not at all inconsistent with its position in this case. Pfizer acknowledges that the '909 patent covers amlodipine besylate, but argues, and in this Court's view, argues persuasively, that the besylate salt of amlodipine is not disclosed by the '909 patent. This is the precise thesis set out in *In re Benno*, at 768 F.2d 1340 at 1346, Fed. Cir. 1985. This distinction is critical and not considered by Apotex, as the Court has now properly analyzed whether the '909 patent anticipates the '303.

Obviousness.

An invention cannot be patented if, in light of the prior art, the invention is obvious to one having ordinary skill in the art to which the patent pertains. I reference 35 U.S.C. Section 103(a). Here, the Court is called upon to define the person having reasonable skill in the art.

The Court finds that a person having ordinary skill in the art would have a bachelor's degree in pharmaceutical science or analytical chemistry, and some experience in drugs and drug preparation. For these purposes, the Court also assumes the person having ordinary skill in the art would also have the knowledge of organic chemistry. The Court rejects the suggestion offered by Apotex's expert, Dr. Cima, that a

person having ordinary skill would also possess an understanding of materia science and hydrolytic chemistry. This addition is rejected because it calls for expertise by hindsight. Pfizer and the world now know that amlodipine maleate could not be used to produce a stable commercial product. And we now know this is because of amlodipine maleate's exposure to water that when it is exposed to water, it undergoes a hydrolytic reaction, under which the product breaks down by the mechanism of the Michael Addition reaction, with resulting, ah, unsuitable, ah, byproducts. But all of this was unknown at the time of the '909 patent, when the future of amlodipine maleate was bright. Ultimately, the problem was hydrolytic, but it is only known and now made clear by hindsight. The requirement of hydrolytic chemistry is not a part of one skilled in the art at the time of the grant of the '909 patent. Finally on this point, I do note that under such a strict standard, the inventors themselves would not have possessed the ordinary skill to produce or understand their own art. But even were I to accept it, I do not find that that would lead a person to the obvious conclusions.

To show that the '303 patent is obvious, the defendant must show: One, the prior art suggests to those of ordinary skill in the art that they should make the claimed composition; and two, the prior art suggests a reasonable expectation of success. Here I cite *In re Vaeck*, 947 F.2d 488 at 493, Fed. Cir. 1991. The '303 patent's file wrapper shows that the examiner originally rejected the claimed invention because of obviousness. Under these circumstances, of course, the Court must accept that the defendant has made a prima facie showing on this question.

But this prima facie showing can be rebutted if the patentee can show that the invention has unexpectedly superior outcomes over the prior art. This requires a showing that the claimed invention is an improvement over the prior art, and the improvement was unexpected. I reference *In re Soni* at 54 F.3d 746 at 751, Fed. Cir. 1995; and *In re May* at 574 F.2d 1082 at 1094 and 5, CCPA 10 -- or 1978.

In this regard, Apotex claims again that the universe of pharmaceutically acceptable acid addition salts is small enough to render the use of one or another of them obvious. In doing so, they rely upon the Berge article to show that benzene sulphonate was a known FDA-approved salt -- or anion.

Though a known anion, it remains imperative to note that it reveals that benzene sulphonate, as noted before, was used in only .25 percent of the occurrences prior to the time of 1974. The patent examiner cannot have been aware of the Berge article as it was specifically noted and cited in the '303 patent itself. As such, the Court could not possibly find by clear and convincing evidence that the article and its teachings could not have been considered by the patent when ultimately determining whether the '303 patent was obvious, and in the examiner's determination that it was ultimately not obvious. The Berge article's listing of salt does not render the patent obvious.

The Berge article, however, is particularly enlightening on an additional point. As noted above and accepted by each of the experts who testified, quote: There is no reliable way of predicting the influence of a particular salt species on the behavior of a parent compound, close quote. That is from Berge on page 1. In essence, the formulation of a pharmaceutical salt is a trial and error process, with no guarantee, let alone an expectation of its success.

As to whether the besylate salt is an actual improvement over the maleate, the Court recognizes that while not superior to the maleate salt in every category, the besylate salt clearly and unexpectedly illustrates a superior combination of properties when compared to what was suggested as the preferred preparation, the maleate salt in the '909 patent. In addition to the evidence supplied by the exhibits in the patent, the Court notes the objective consideration that Pfizer would not have changed from the

maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason. I find that the besylate salt was superior to the art.

And turning to inequitable conduct, the defendant argues that the '303 patent is unenforceable, because plaintiff Pfizer engaged in inequitable conduct before the Patent Office, in violation of its duty of candor, and its obligations of truth set forth at 37 C.F.R. Section 1.56.

Again, one seeking to invalidate a patent must prove this proposition by clear and convincing evidence. I cite for this proposition, and once again there are many cases setting it forth, *Allied Colloids v. American Cyanamid* at 64 F.3d 1570, 1578, Fed. Cir. 1995. Here a defendant is required to show both failure to disclose information material to patentability or intentional misrepresentation of a material fact and intent to deceive the Patent Office. Citing *Kingsdown v. Hollister* at 863 F.2d 867 at 872, Fed. Cir. 1988. Quoting here: After finding threshold levels of materiality and intent, the trial court must balance the two and determine in its discretion whether inequitable conduct has occurred, closing the quote. That's *Amgen v. Chugai* at 927 F.2d 1200 at 1215, Fed. Cir. 1991.

The defendant has identified several statements in the patent they argue are material misrepresentations, many of which have been referred to, and the Court resets its findings as previously set forth in this opinion's prior recitation. Apotex alleges the solubility of the besylate salt is fraudulently identified in the patent to be 4.6, while Pfizer documents show it to be 3.5 milliliters per, or milligrams per milliliter. The patent claims a thousand tablets were tested for processability, while Pfizer documents show varying numbers up to 150. And the patent's ordinal method of ranking stability is somehow fraudulent upon the Patent Office because it does not reveal that the differences between the besylate, tosylate, and mesylate are minor.

The Court, at the outset, records its findings that these are simply not material concerns. But even assuming that they were, the Court finds that while defendant has shown minor discrepancies between known research and the terms of the patent, the defendant has not shown any of the statements in the patent to be false. As previously noted, amlodipine besylate solid -- solubility is certainly above the 1.0 milligram per milliliter level which is the sought-after solubility. As for stability, the besylate maintains its integrity and is far better than the maleate, which suffers, as I've indicated, the Michael Addition reaction, which is part of the relevant prior art.

The Court finds that Apotex has failed to show anything approaching clear and convincing evidence touching the second element, intent to defraud. There is precious little evidence at all which might be claimed to show an intent to deceive on behalf of Pfizer. The missing notebooks, while troublesome, do not show an intent to deceive. While it is clear Pfizer was eager to extend the patent life of its amlodipine compound, such a desire does not rise to the level of fraudulent intent.

The proof in this Court's -- in this patent's worth is in the pudding. The besylate salt works, and it has been incredibly successful. No matter how valuable the discovery of amlodipine, it is useless, useless to the point of nearly being rejected for pharmacological use, until the discovery, and the Court finds it to be an exceptional discovery, the besylate salt which finally produced a reliable delivery system.

Amlodipine besylate is an invention in its own right, unanticipated, not obvious, and patented in good faith. The '303 patent is valid, enforceable, and would be infringed unless the defendants are restrained from producing their proposed product prior to the expiration of the '303 patent term. The Court finds as a matter of law that the defendants

have committed an act of infringement in filing an Abbreviated New Drug Application seeking to produce amlodipine besylate prior to that date. They will be enjoined from further proceedings in that regard. And that will be the order of the Court. I thank you.

***

APPENDIX

UNITED STATES COURT OF APPEALS, FEDERAL CIRCUIT.

PFIZER, INC.,
Plaintiff-Appellee,

v.

APOTEX, INC. (FORMERLY KNOWN AS TORPHARM, INC.),
Defendant-Appellant.

NO. 2006-1261.

DECIDED: MARCH 22, 2007.

Before MICHEL, Chief Judge, MAYER, and LINN, Circuit Judges.

MICHEL, Chief Judge.

Pfizer Inc. filed suit against Apotex, Inc. (formerly known as TorPharm, Inc.) in the United States District Court for the Northern District of Illinois on July 30, 2003, alleging that, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Apotex's filing with the United States Food and Drug Administration ("FDA") of its Abbreviated New Drug Application ("ANDA") No. 76-719 seeking approval to commercially sell amlodipine besylate tablets (2.5 mg, 5 mg, and 10 mg strengths) before the expiration of the term of U.S. Patent No. 4,879,303 ("the 303 patent") to Pfizer, infringed claims 1-3 of the 303 patent. The ANDA product sought to be approved by Apotex is a generic version of Pfizer's amlodipine besylate drug product, which is commercially sold in tablet form in the United States under the trademark Norvasc® . Norvasc® is approved by the FDA for treating

hypertension and chronic stable and vasospastic angina. The 303 patent, entitled "Pharmaceutically Acceptable Salts," is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") with respect to the Norvasc® drug product in accordance with 21 U.S.C. § 355(b)(1). Apotex certified in ANDA No. 76-719 that it believed the 303 patent was invalid and unenforceable, and sought approval to market and sell its amlodipine besylate tablets before September 25, 2007 (i.e., the expiration date of the 303 patent plus an additional six months of pediatric exclusivity) pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

In its answer to Pfizer's complaint, Apotex denied infringement and counterclaimed for declaratory judgments that the claims of the 303 patent are invalid for anticipation and obviousness, and that the 303 patent is unenforceable due to Pfizer's alleged inequitable conduct before the United States Patent and Trademark Office ("USPTO"). Prior to trial, however, Apotex stipulated that its ANDA product contains each limitation of claims 1-3 of the 303 patent, and that if the 303 patent were upheld as valid and enforceable, its ANDA product would literally infringe those claims.

Following a bench trial, the district court entered a final judgment on January 29, 2006 for Pfizer and against Apotex on Apotex's request for declaratory judgments that the claims of the 303 patent are invalid or unenforceable. Based on the stipulation, the trial court found infringement. The district court then ordered that the effective date of any approval of Apotex's ANDA No. 76-719 shall not be earlier than September 25, 2007, and enjoined Apotex from making, using, offering to sell, selling, or importing into the United States any product comprising amlodipine besylate covered by (or the use of which is covered by) the claims of the 303 patent until September 25, 2007. *Pfizer Inc. v. Apotex, Inc.*, No. 03C 5289 (N.D.Ill. Jan. 29, 2006).

Pfizer dismissed its claim of willful infringement against Apotex by a Stipulation and Order dated January 23, 2006. Apotex now appeals from the district court's final judgment, challenging the rulings as to validity and enforceability. Because the district court erred in holding that the subject matter of claims 1-3 of the 303 patent would not have been obvious, we reverse. We therefore do not address Apotex's assertion that it had proven that Pfizer engaged in inequitable conduct before the USPTO during prosecution of the 303 patent.

I. BACKGROUND

A.

Norvasc® contains amlodipine besylate. The active ingredient found in Norvasc® is 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, commonly referred to as amlodipine. Amlodipine is a member of a class of compounds referred to as dihydropyridines. Active drug molecules, such as amlodipine, are frequently made into pharmaceutically-acceptable acid addition salts to improve their bioavailability. Amlodipine besylate [1] is an acid addition salt form of amlodipine, formed from the reaction of amlodipine, a weak base, and benzene sulphonic acid.

Pfizer's Discovery Chemistry group, located in Sandwich, England, invented amlodipine and discovered its anti-hypertensive and anti-ischemic pharmacological properties prior to 1982. Pfizer filed a patent application in the United Kingdom on March 11, 1982 specifically claiming amlodipine. A U.S. counterpart application claiming priority

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[1] Besylate is referred to in the art interchangeably as benzene sulphonate, benzenesulphonate, or benzene sulfunate.

from the U.K. application issued as U.S. Patent No. 4,572,909 ("the 909 patent") on February 25, 1986.[2] The 909 patent claims certain dihydropyridine compounds and their pharmaceutically-acceptable acid addition salts. The 909 patent discloses that the pharmaceutically-acceptable acid addition salts of amlodipine "are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts," and that the preferred salt is maleate.[3] 909 patent col.2 ll.3-10.

Meanwhile, on or about July 14, 1982, the Discovery Chemistry group recommended that amlodipine be developed as a commercial drug product. By this time, Pfizer had made several acid addition salts of amlodipine, including the maleate, fumarate, salicylate, hydrochloride, and methane sulphonate forms. The Discovery Chemistry group designated amlodipine maleate as the drug substance for development.

On or about August 11, 1982, the project of formulating a commercial drug product was assigned to Dr. James Wells, a manager in Pfizer's Pharmaceutical Research and Development Department, who was assisted by Mr. Edward Davison, a member of the same group. By April 24, 1984, Dr. Wells identified a formulation for amlodipine

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[2] The 909 patent was subject to an appeal before this court in *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361 (Fed.Cir.2004). There, this court held that the term of the 909 patent as extended under the patent term restoration provision of the Hatch-Waxman Act covers amlodipine and any salt or ester as claimed in claims 1, 7, and 8. *Id.* at 1367.

[3] We recognize that hydrochloride and hydrobromide are not technically anions. However, since the patentee chose to be his own lexicographer, we will refer to these two acids as anions for purposes of this opinion. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed.Cir.2005) (en banc).

maleate that produced "excellent capsules." In attempting to produce a direct compression tablet product of an amlodipine maleate formulation, however, Dr. Wells encountered two problems: (1) chemical instability of the amlodipine maleate, and (2) stickiness of the tablet blend of amlodipine maleate. Chemical stability refers to the resistance of a drug compound to chemical breakdown, while stickiness refers to the adherence of the drug substance, in formulation, to manufacturing equipment, such as the punch faces of a tablet-making press.

To solve the problems of the tablet form of amlodipine maleate, Dr. Wells suggested that other amlodipine salts be made and tested. In a memo dated April 24, 1984, Dr. Wells acknowledged the difficulty in stickiness and stability he was experiencing in attempting to make a tablet formulation of amlodipine maleate and stated that, by changing from the maleate salt to the free base of amlodipine or another acid addition salt, "many of the stability problems would disappear." Dr. Wells identified six alternative anions, i.e., hydrochloride, methane sulphonate, benzene sulphonate, lactate, succinate, and acetate, as potential anions with which to create acid addition salt forms of amlodipine. He also eventually added the tosylate anion to this group. Dr. Wells testified at trial that he selected these candidates based on their differing structures and properties, but could not explain why three of the seven alternative anions were members of the same class of sulphonic acids.

Mr. Davison testified at trial that he tested these amlodipine acid addition salt forms as well as amlodipine maleate and the free base for solubility, pH, hygroscopicity, and stickiness. Another researcher, Dr. Robin Platt, an analytical chemist at Sandwich, was brought in to test the stability of the amlodipine acid addition salts. Dr. Platt subjected the maleate, acetate, succinate, besylate, mesylate, and eventually the tosylate, salicylate, and hydrochloride salt forms of amlodipine to thin-layer chromatography to determine the number and amount of degradants found in the

various amlodipine salts, and compiled a ranking thereof based upon the stability of each salt formulation.

Dr. Platt's findings were communicated to Dr. Wells via memorandum on or about October 9, 1984, wherein Dr. Platt reported that the besylate salt "showed a much improved stability profile over the maleate in all cases." On October 11, 1984, Dr. Wells recommended via memorandum to Dr. J.R. Davidson, a deputy of Pfizer's Pharmaceutical Research and Development Department, that the amlodipine maleate salt be replaced with amlodipine besylate for the commercial amlodipine tablet product based on Dr. Platt's memo and Mr. Davison's test results.

By April 30, 1985, both amlodipine maleate and amlodipine besylate were undergoing human testing in clinical trials. Pfizer scientists predicted that the capsule form of amlodipine maleate would have a shelf life of three years, but that "poor stability of amlodipine maleate tablet formulations" precluded commercialization. On the other hand, the scientists noted that amlodipine besylate tablet formulations exhibited "clear superiority" in their processing characteristics, particularly non-stickiness, and in stability. Capsule formulations of amlodipine besylate had not yet been produced, but work on this project was "expected to be straightforward."

On April 4, 1986, Pfizer filed a patent application to amlodipine besylate in the U.K., which eventually issued as U.K. Patent No. 160833. On May 5, 1986, Pfizer submitted a supplement to the FDA stating that the dosage form anticipated for commercial use would be a tablet of amlodipine besylate and that all future clinical trials with amlodipine would use this new formulation. In the supplement, Pfizer stated, "We feel that the change in salt form is justified since benzenesulfonate is a commercially acceptable salt, as exemplified by the tranquilizer mesoridazine (Serentil)." In support of the use of the

besylate salt form of amlodipine, Pfizer submitted a summary of the acute oral toxicity of amlodipine besylate and amlodipine maleate in rats and a comparison of the effects of both the besylate and maleate forms on blood pressure and heart rate of dogs. Pfizer stated that the results showed that there was no quantitative difference in efficacy between equivalent doses of amlodipine besylate tablets or capsules and amlodipine maleate capsules. In addition, Pfizer submitted a pharmacokinetic report and interim clinical summary showing that amlodipine besylate tablets and amlodipine maleate capsules were bioequivalent and had comparable safety and toleration when administered to healthy human volunteers.

On March 25, 1987, Pfizer filed a U.S. application (serial no. 07/030,658) to amlodipine besylate claiming priority from the U.K. application. During prosecution, the examiner initially rejected all claims of the application as obvious over the 909 patent in view of U.S. Patent 4,032,637 to Spiegel (1977) ("Spiegel") and U.S. Patent 3,816,612 to Schmidt (1974) ("Schmidt"). The examiner noted that Schmidt discloses that aryl sulphonic acid salts, which include besylate, are superior to the preferred maleate of the '909 patent, while Spiegel provides an example of a pharmaceutical compound wherein the besylate form is specifically identified as the preferred embodiment. In response to the rejection, Pfizer argued that the besylate salt,

> while *not* the most soluble salt, has many other advantages not possessed by other acid addition salts.... [I]n addition to having good solubility, [the besylate salt] is unique in imparting to the product good stability, nonhygroscopicity and good processability. For one salt to have all of these outstanding features is not suggested or taught in the art, and would require extensive experimentation to find.

The examiner, however, maintained the rejection, stating that "these qualities are basic considerations by a person skilled in the art for selecting a suitable pharmaceutical salt" as evidenced by Berge, "Pharmaceutical Salts," *J. Pharm. Sci.*, 66(1):1-19 (Jan.1977) ("Berge"). Table 1 of Berge shows 53 FDA-approved, commercially marketed anions, including benzene sulphonate, that are useful for making pharmaceutically-acceptable salts, and lists the relative frequency of which each was used as a percentage based on the total number of anions or cations in use through 1974. Berge discloses that benzene sulphonate had a frequency of use of 0.25%.

In response to a final obviousness rejection by the Examiner, Pfizer filed a continuation application (serial no. 07/256,938) and abandoned the original application. Along with the continuation application, Pfizer submitted a preliminary amendment and statement, and a declaration under 37 C.F.R. § 1.132 by Dr. Wells dated October 3, 1988 ("Wells Declaration"). In the statement, Pfizer argued that the Wells Declaration demonstrated that the besylate salt of amlodipine possessed "*all* the desired characteristics necessary for a medicinal agent" and that it would not have been obvious "that only the besylate salt of amlodipine would have all the necessary properties for a commercial product." Pfizer argued that choosing an appropriate salt is a very difficult task "since each salt imparts unique properties to the parent compound" and that one skilled in the art would "conclude that the besylate salt of amlodipine is a unique compound and not an obvious one." The Wells Declaration stated that the besylate salt of amlodipine was "found to possess a highly desirable combination of physicochemical properties," including good solubility, stability, non-hygroscopicity, and processability, which properties are "unpredictable both individually and collectively."

The continuation application was allowed and issued as the 303 patent on November 7, 1989. The first three claims of the 303 patent are reproduced here:

1. The besylate salt of amlodipine.

2. A pharmaceutical composition comprising an anti hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically-acceptable diluent or carrier.

3. A tablet formulation comprising an anti-hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.

Norvasc® was launched as a commercial product by Pfizer in the U.S. in November 1992.

B.

From January 11, 2006, to January 18, 2006, the district court conducted a bench trial on the issues of (1) whether the claims of the 303 patent were anticipated by the disclosure of the 909 patent, (2) whether the 303 patent was invalid for obviousness, and (3) whether the claims of the 303 patent were unenforceable due to inequitable conduct before the USPTO. On January 18, 2006, the district court stated its findings and conclusions pursuant to Fed.R.Civ.P. 52(a) orally in open court. *Bench Order Tr.* 1-28, January 18, 2006. The district court concluded that Apotex failed to meet its burden of proving invalidity or inequitable conduct by clear and convincing evidence.

The district court first addressed the issue of invalidity by anticipation, finding that while the 909 patent claims a genus of pharmaceutically-acceptable salts of amlodipine that encompasses amlodipine besylate, the 909 patent does not as a matter of law disclose it. The district court held that since the 909 patent does not list the species

of a salt made from benzene sulphonate, it does not anticipate the claims of the 303 patent.

With regard to obviousness, the district court rejected Apotex's argument that the 909 patent in view of the Berge article (and other prior art) rendered the invention of the claims of the 303 patent obvious. The district court first found that a person of ordinary skill in the art would have a bachelor's degree in pharmaceutical science or analytical chemistry, and some experience in drugs and drug preparation. The district court concluded that the Berge article does not direct the skilled artisan to create the besylate salt of amlodipine because Berge discloses that benzene sulphonate was used only at a frequency of 0.25%, or 1 out of every 400 drugs, prior to 1974. The district court noted that the examiner must have considered the Berge article since it was cited in the 303 patent, yet the examiner ultimately determined that the claims of the 303 patent were not obvious in view of this reference.[4] Further, the district court stated that there would be no expectation of success in making a besylate salt of amlodipine because, as Berge teaches and expert testimony on both sides accepted, "There is no reliable way of predicting the influence of a particular salt species on the behavior of a parent compound." *Bench Order Tr.* 23:3-6.

The district court also stated that the besylate salt of amlodipine was unexpectedly superior to the amlodipine salts of the prior art. Specifically, the district court stated that,

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[4] The trial transcript reads, "The patent examiner cannot [sic] have been aware of the Berge article as it was specifically noted and cited in the 303 patent itself. As such, the Court could not possibly find by clear and convincing evidence that the article and its teachings could not have been considered by the patent [sic] when ultimately determining whether the 303 patent was obvious...." *Bench Order Tr.* 22:16-22. We interpret this passage in the only way that makes sense-that the Examiner did consider the Berge reference during prosecution. While oral bench rulings are certainly authorized, they may be ill-advised in a case of this complexity.

while amlodipine besylate was not superior to amlodipine maleate "in every category," it nonetheless "clearly and unexpectedly illustrates a superior combination of properties when compared to what was suggested in the preferred preparation"-- ostensibly the amlodipine maleate disclosed as the preferred embodiment of the 909 patent. These properties included good solubility, stability, non-hygroscopicity, and processability (non-stickiness). The district court found that amlodipine besylate exhibited at least a solubility exceeding 1.0 mg/ml, which the court stated is the desirable solubility factor for a commercial product, and that the 303 patent listed the besylate salt form of amlodipine as the most stable salt form out of eight salts tested, with the maleate salt form being sixth on the list.

The district court also rejected Apotex's argument that amlodipine besylate is actually hygroscopic rather than non-hygroscopic as disclosed in the 303 patent. Apotex asserted that amlodipine besylate attracts water because it (1) can exist as a hydrate, (2) may have water within its crystalline structure, and (3) can have water on its surface at extended temperatures and humidity. The district court stated that while each of these facts is true, each was entirely unenlightening because hygroscopicity per se was not a critical factor. Instead, the district court emphasized that the maleate salt of amlodipine underwent a Michael addition reaction when exposed to water, creating at least ten degradation products making amlodipine maleate unsuitable at least in tablet form for medicinal purposes, whereas the amlodipine besylate did not undergo the same reaction. Lastly, the district court found that Pfizer conducted extensive tests for processability of the amlodipine besylate by manufacturing tablets on conventional tablet-making machinery and measuring the amount of product sticking to the punch face after each manufacturing run. The district court concluded that the tests showed that amlodipine besylate was sufficiently non-sticky so as to be commercially processable and less sticky than the maleate form.

Besides evidence of superiority provided in the 303 patent itself, the district court pointed to another "objective consideration" in determining that amlodipine besylate was not obvious over the prior art: "Pfizer would not have changed from the maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason." *Bench Order Tr.* 23:16-21. For all these reasons, the district court held that the claims of the 303 patent were not proven invalid for obviousness.

Next, the district court rejected Apotex's claim that Pfizer engaged in inequitable conduct before the USPTO in violation of its duty of candor and 37 C.F.R § 1.56. Apotex argued that Pfizer made several material misrepresentations to the USPTO during prosecution of the application leading to the 303 patent, including misrepresenting the solubility, stability, and hygroscopicity of amlodipine besylate and misrepresenting the number of tablets tested for processability both in the patent application and in the Wells Declaration. Specifically, Apotex asserted that Pfizer (1) fraudulently identified the solubility of amlodipine besylate in its application for patent as 4.6 mg/ml where internal Pfizer documents show the solubility to actually be 3.5 mg/ml; (2) fraudulently claimed in the application to have tested over a thousand tablets for stickiness where internal Pfizer documents show varying numbers up to only 150 tablets were actually tested; and (3) fraudulently ranked the respective stabilities of the various salt forms of amlodipine in an ordinal-rather than quantitative-fashion so as to conceal from the USPTO that the stability differences between the besylate, tosylate, and mesylate salt forms of amlodipine were actually very minor.

The district court first determined that none of these alleged misrepresentations were either material or false. In this regard, the court stated that whether the solubility of amlodipine besylate is 4.6 mg/ml as identified in the 303 patent or 3.5 mg/ml as identified in internal Pfizer documents

was at most a minor discrepancy given that any solubility over the critical 1.0 mg/ml level was sufficient solubility to meet the standards of a drug company seeking to produce a commercial drug. As for stability, the district court found that amlodipine besylate was far more stable than amlodipine maleate, which as described above undergoes the undesirable Michael addition reaction. Second, the district court held that Apotex failed to show intent to deceive by clear and convincing evidence. Indeed, the court found "precious little evidence at all" showing an intent to deceive, stating that "[w]hile it is clear that Pfizer was eager to extend the patent life of its amlodipine compound, such a desire does not rise to the level of fraudulent conduct." *Bench Order Tr.* 25:24-26:1.

On January 29, 2006, the district court entered a final judgment in favor of Pfizer and against Apotex on Pfizer's claim of infringement as well as on Apotex's counterclaims alleging and seeking declarations of invalidity and unenforceability of the 303 patent. The district court also ordered that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Apotex's ANDA No. 76-719 shall not be earlier than September 25, 2007, and pursuant to 35 U.S.C. § 271(e)(4)(B), enjoined Apotex, its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with it, from engaging in the manufacture, use, offer for sale, or sale within the U.S., or importation into the U.S. of any product comprising amlodipine besylate covered by, or the use of which is covered by, the claims of the 303 patent until September 25, 2007. *Pfizer Inc. v. Apotex, Inc.*, No. 03C 5289 (N.D.Ill. Jan. 29, 2006). On February 17, 2006, Apotex filed a timely notice of appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

A.

Apotex appeals the district court's final judgment that it failed to prove by clear and convincing evidence that the invention of claims 1-3 of the 303 patent would have been obvious and are therefore invalid, and the district court's finding that Apotex failed to prove Pfizer committed inequitable conduct before the USPTO. Because the district court erred in holding non-obvious the invention of claims 1-3 of the 303 patent, we reverse the district court's judgment. Since we hold that claims 1-3 are invalid for obviousness, we need not and do not address Apotex's assertion that Pfizer engaged in inequitable conduct before the USPTO during prosecution of the 303 patent.

On appeal from a bench trial, this court reviews the trial court's conclusions of law de novo and findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed.Cir.2004). The ultimate conclusion of whether a claimed invention would have been obvious is a question of law reviewed de novo based on underlying findings of fact reviewed for clear error. *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed.Cir.1997). A factual finding is clearly erroneous if, despite some supporting evidence, "the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395, 68 S.Ct. 525, 92 L.Ed. 746 (1948).

B.

The district court held that Apotex had established a prima facie case of obviousness because the patent examiner initially rejected the claims to amlodipine besylate for obviousness. Specifically, the district court stated, "The

303 patent's file wrapper shows that the examiner originally rejected the claimed invention because of obviousness. Under these circumstances, of course, the Court must accept that the defendant has made a prima facie showing on this question." *Bench Order Tr.* 21:20-24. The district court's ruling must be rejected, not only because it is legally incorrect, but also because it may reflect a serious misconception regarding the proper burden of proof each party bears in a patent litigation.

Our case law consistently provides that a court is never bound by an examiner's finding in an ex parte patent application proceeding. *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1555 (Fed.Cir.1985). Thus, it can never be the case that an examiner's interim finding of prima facie obviousness renders the claims of an issued patent prima facie obvious. Instead, deference to the decisions of the USPTO takes the form of the presumption of validity under 35 U.S.C. § 282. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1329 (Fed.Cir.2000). That is, by statute a patent is valid upon issuance, 35 U.S.C. § 282, and included within the presumption of validity is a presumption of non-obviousness. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 714 (Fed.Cir.1984). Since we must presume a patent valid, the patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence. [5] That burden of proof never shifts to the patentee to prove validity. *Hybritech Inc. v. Monoclonal*

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[5] The "clear and convincing" standard is an intermediate standard which lies somewhere in between the "beyond a reasonable doubt" and the "preponderance of the evidence" standards of proof. *Addington v. Texas*, 441 U.S. 418, 425, 99 S.Ct. 1804, 60 L.Ed.2d 323 (1979); *see also SSIH Equip. S.A. v. United States Int'l Trade Comm'n*, 718 F.2d 365, 380-81 (Fed.Cir.1983) (Nies, J., additional views). Although an exact definition is elusive, "clear and convincing evidence" has been described as evidence that "place[s] in the ultimate factfinder an abiding conviction that the truth of its factual contentions are highly probable." *Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433, 81 L.Ed.2d 247 (1984) (internal quotations omitted).

Antibodies, Inc., 802 F.2d 1367, 1375 (Fed.Cir.1986). "The presumption [of validity] remains intact and [the burden of proof remains] on the challenger throughout the litigation, and the clear and convincing standard does not change." *Id.*

It is true that once a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence. *See Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1216 (Fed.Cir.1998) (citing *Hybritech*, 802 F.2d at 1376); *Cable Elec. Prods. Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1022 (Fed.Cir.1985) ("[I]f evidence is presented establishing a prima facie case of invalidity, the opponent of invalidity must come forward with evidence to counter the prima facie challenge to the presumption of section 282."). But, all that means is that even though a patentee never *must* submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity-what we call a prima facie case-the patentee "would be well advised to introduce evidence sufficient to rebut that of the challenger." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1570 (Fed.Cir.1986).

However, this requirement does not "in substance shift the burden of persuasion," *Cable Elec.*, 770 F.2d at 1022, because "the presumption of validity remains intact and the ultimate burden of proving invalidity remains with the challenger throughout the litigation." *Mas-Hamilton Group*, 156 F.3d at 1216; *see also Innovative Scuba Concepts, Inc. v. Feder Indus., Inc.*, 26 F.3d 1112, 1115 (Fed.Cir.1994); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 287 (Fed.Cir.1985). The trial court has the responsibility to determine whether the challenger has met its burden by clear and convincing evidence by considering the totality of the evidence, including any rebuttal evidence presented by the patentee. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed.Cir.1983).

The *basis* (as opposed to the mere existence) of an examiner's initial finding of prima facie obviousness of an issued patent is therefore, at most only one factual consideration that the trial court must consider in context of the totality of the evidence "in determining whether the party asserting invalidity has met its statutory burden by clear and convincing evidence." *Fromson,* 755 F.2d at 1555. It does not, however, lessen or otherwise affect the burden of proof, nor does it require that unless the patentee introduces evidence of secondary considerations to establish non-obviousness, the patent challenger will necessarily prevail.

C.

The underlying factual determinations made by the trial court that this court must review for clear error include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). We start by noting that the parties stipulated to many of the facts, but disagree as to the ultimate legal outcome of obviousness based upon those facts. The parties do not dispute that benzene sulphonate was known in the art at the time of the inventions claimed in the 909 and 303 patents. Pfizer admitted that several publications, including the Berge article, were prior art to claims 1-3 of the 303 patent and pertinent to the problem the inventors sought to overcome. Neither party disputes the district court's characterization of the ordinarily skilled artisan.

Further, there is really no dispute as to the scope of the 909 patent and the differences between it and the claimed invention. The 909 patent specifically states that the pharmaceutically-acceptable salts of amlodipine "are those formed from acids which form non-toxic acid addition salts

containing pharmaceutically-acceptable anions." 909 patent col.2 ll.3-6. The 909 patent lists a genus of pharmaceutically-acceptable anions "such as the hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate." 909 patent col.2 ll.6-9. The only examples of acid addition salts of amlodipine are maleates. The 909 patent does not expressly disclose the benzene sulphonate anion nor salts formed from benzene sulphonic acid or a larger class of sulphonic acids in general. But, while neither the claims nor the written description of the 909 patent expressly disclose amlodipine besylate or the benzene sulphonate anion, neither do they exclude amlodipine besylate or the benzene sulphonate anion. Rather, the only limitations placed on the anion are that it is pharmaceutically-acceptable, and that in salt form, it is able to produce a non-toxic acid addition salt. Thus, as the district court found and the parties agree, the 909 patent claims literally encompass amlodipine besylate.

By statute, a claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Subsumed within the *Graham* factors is a subsidiary requirement articulated by this court that where, as here, all claim limitations are found in a number of prior art references, the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so. *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed.Cir.2006); *Velander v. Garner*, 348 F.3d 1359, 1363 (Fed.Cir.2003). Here, the parties vigorously disagree.

A difficulty in the district court's opinion arises because, in assuming a prima facie case of obviousness, the

district court did not fully address whether Apotex showed by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references relied on, especially the 909 patent and Berge, to achieve the claimed invention. However, the district court's omission in this case is harmless error because evidence of record easily satisfies us that a reasonable fact-finder could only conclude that Apotex has shown by clear and convincing evidence that the skilled artisan would indeed have been so motivated to combine the prior art to produce the besylate salt of amlodipine. The record also satisfies us that, contrary to the district court's finding, a reasonable fact-finder could only conclude that the skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine for the reasons elaborated, post.

Motivation to Combine Prior Art References to Achieve the Claimed Invention

Pfizer does not argue that there was no motivation to combine the prior art references per se. Rather, Pfizer argues that (1) the 909 patent does not suggest or motivate the skilled artisan to make amlodipine besylate because none of the anions listed in the 909 patent have a cyclic structure as does besylate, and (2) even if the 909 patent were combined with Berge, the skilled artisan would not have been motivated to make amlodipine besylate because Berge shows that besylate was actually one of the most rarely used anions in the pharmaceutical industry, as only 0.25% of approved drugs as of 1974 were besylate salts. Finally, Pfizer asserts that other prior art references relied upon by Apotex are not relevant because the examples of besylate salts disclosed in these references are limited to pharmaceuticals unrelated to amlodipine.

We reject Pfizer's first argument, since a suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to

be found explicitly in the prior art references sought to be combined, but rather "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *DyStar*, 464 F.3d at 1361; *see also Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1307-08 (Fed.Cir.2006). In other words, it is irrelevant that none of the anions specifically listed in the 909 patent have a cyclic structure, because the motivation to make amlodipine besylate here is gleaned not only from the prior art as a whole rather than the 909 patent alone, but also from the nature of the problems encountered with the amlodipine maleate tablet formulations sought to be solved by the inventors of the 303 patent. In this regard, testimony of record evidences that one skilled in the art would have been motivated to choose an anion having a different structure than that of maleate. The maleate salt ion is acyclic and consists of a double bond between the carbon atoms, whereas the besylate salt ion is cyclic and lacks the same double bond. Early in development, Pfizer discovered that amlodipine maleate was susceptible to degradation from a Michael addition reaction in which the double bond of maleate underwent an addition reaction causing the formation of degradation products. Apotex avers that unrebutted testimony from its expert, which we find compelling, supports an inference that the skilled artisan actually would have been encouraged, rather than discouraged, to choose an anion without the same double bond, such as benzene sulphonate, in order to avoid the Michael addition reaction. Thus, the fact that none of the anions listed in the 909 patent have a cyclic structure is hardly dispositive to the question of whether the skilled artisan would have been motivated to combine the prior art references to achieve amlodipine besylate.

We similarly are not persuaded by Pfizer's second argument, as clear and convincing evidence shows that a skilled artisan would have been motivated to combine the 909 patent and Berge to make amlodipine besylate. Pfizer's expert, Dr. Anderson, testified that there were an unlimited

number of anions, many of which could be used to form pharmaceutically-acceptable acid addition salts. Yet a reasonable fact-finder could not accept Dr. Anderson's testimony that the number of acceptable anions was "unlimited." Of course, new salts can always be made or attempted. However, irrefutable evidence shows that a skilled chemist at the time would simply make *known* pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time. Indeed, Mr. Davison, an inventor of the 303 patent, testified that it "would have been a mistake" to choose a novel anion. Rather, "part and parcel of pharmaceutically accepted[ ] was to look in pharmacopoeias and compendia" to find an anion having "precedence for use within the pharmaceutical industry." Dr. Anderson similarly admitted in his testimony that it would have been logical to use Berge's list of FDA-approved anions to produce a drug formulation:

> Court: What if I sic my phalanx of zealous scientists on that list and then come up with a product. Would that be a logical thing for me to do? The Witness: It would be logical to try that.

This is true especially given the fact that the genus of FDA-approved anions at the time was small, i.e., only 53. That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as "rarely used." *See* Berge, Table 1 (showing that 40 out of 53 anions were used in less than 1% of drugs and 23 out of 53 were used in 0.25% or less of drugs).

But the outcome of this case need not rest heavily on the size of the genus of pharmaceutically-acceptable anions disclosed by Berge because clear and convincing evidence establishes that, out of the list of 53 anions, one of ordinary skill in the art would have favorably considered benzene

sulphonate because of its known acid strength, solubility, and other known chemical characteristics as reported in several other publications Pfizer has admitted are prior art. Schmidt discloses that aryl sulphonic acids, such as benzene sulphonic acids, considerably increase the solubility of pharmaceuticals containing one or more basically reacting nitrogen atoms. 612 patent col.2 ll.14-41. Spiegel specifically identifies besylate as the preferred pharmaceutically-acceptable acid addition salt form of a pharmaceutical compound. 637 patent col.2 ll.38-39. Other patents not before the examiner during prosecution of the 303 patent also point to benzene sulphonate. U.S. Patent 3,970,662 to Carabateas (1976) ("Carabateas") discloses an intermediate dihydropyridine compound useful in the form of an acid addition salt derived from benzene sulphonate. 662 patent col.3 ll.35-49 & col.4 ll.20-24. U.S. Patent 4,432,987 to Barth (1984) ("Barth"), assigned to Pfizer, discloses the besylate acid addition salt form of a pharmaceutical composition having excellent pharmacokinetic properties, near-optimal solubility, and improved stability. 987 patent col.2 ll.45-46. Taken together, these references provide ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate.

The district court ignored the significance of these other prior art references suggesting the besylate salt because the pharmaceuticals disclosed in those prior art references were not described as useful to treat hypertension or angina, as is amlodipine. By not considering these references in its obviousness analysis, however, the district court clearly erred. As here, the besylate acid addition salt form was described in these prior art references as useful in promoting stability and solubility, as well as improving other physicochemical characteristics. That none of these references discloses a medication for treating hypertension or angina like amlodipine is therefore unimportant, if not actually irrelevant. As Pfizer concedes, the besylate part of the acid addition salt has no therapeutic effect, but merely serves as a means to deliver the amlodipine part of the

molecule to the body. Prior art disclosing the use of benzene sulphonate for improving the bioavailability of other pharmaceuticals-especially a dihydropyridine as disclosed by Carabateas-is therefore highly relevant in weighing the factors relating to obviousness.

Considering all of the evidence, we hold that a reasonable fact-finder could only conclude that Apotex indeed produced clear and convincing evidence that one skilled in the art, facing the problems including the stickiness of the tablet form of the maleate acid addition salt, would have been motivated to combine the teachings of the 909 patent, Berge, and other prior art, to produce the besylate salt of amlodipine.

Reasonable Expectation of Success

As noted above, the district court found that the skilled artisan would have had no expectation of success in making a besylate salt of amlodipine because there was no reliable way to predict the influence of a particular salt species on the active part of the compound. We cannot reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be. The problem with the district court's ultimate conclusion of non-obviousness based on that factual finding, however, is that case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. *See In re Corkill*, 771 F.2d 1496, 1500 (Fed.Cir.1985) ("Although [the inventor] declared that it cannot be predicted how any candidate will work in a detergent composition, but that it must be tested, this does not overcome [the prior art's] teaching that hydrated zeolites will work."); *see also Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed.Cir.2000); *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed.Cir.1989); *In re Merck* & Co., *Inc.*,

800 F.2d 1091, 1097 (Fed.Cir.1986). Indeed, a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt-including those specifically listed in the 909 patent itself-would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute. *Merck,* 874 F.2d at 809; *In re O'Farrell,* 853 F.2d 894, 903 (Fed.Cir.1988).

The evidence would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that an acid addition salt of besylate would form and would work for its intended purpose. *See In re Rinehart,* 531 F.2d 1048, 1053-54 (C.C.P.A.1976). Specifically, the evidence clearly shows that as soon as tablet processing problems arose with the amlodipine maleate tablet formulations, Dr. Wells readily compiled a list of seven alternative anions-including the besylate-each of which he expected would form an amlodipine acid addition salt:

> Q. And one of the reasons why you chose these various salts [sic], or suggested these various salts [sic], is because you expected that they would be able to make a salt of them, correct?
>
> A. There was an expectation, but that wasn't guaranteed.

But, once again, only a reasonable expectation of success, not a guarantee, is needed. *O'Farrell,* 853 F.2d at 903; *Brown & Williamson,* 229 F.3d at 1125. That reasonable expectation of success is further amply reflected in Dr. Wells' further testimony that he expected these seven amlodipine acid addition salts would show improved physicochemical characteristics over the maleate salt, including improved stability and non-stickiness:

> Q. And when you chose these salts ... you believed that if you could, in fact, make an amlodipine salt out of them, these might be a cure for the problems you were having with maleate, correct?
>
> A. Indeed.

We also note that the 909 patent placed no limitations on the acid addition salt whatsoever, except that it be non-toxic and formed from an acid containing a pharmaceutically-acceptable anion. Accordingly, the 909 patent contained a strong suggestion that any and all pharmaceutically-acceptable anions would form non-toxic acid addition salts and would work for their intended purpose-that is, to improve bioavailability of the active ingredient amlodipine and to improve handling and storage of amlodipine. Indeed, in proceedings before this court in *Pfizer v. Dr. Reddy's Laboratories* involving the 909 patent, Pfizer downplayed any difference between amlodipine maleate and any other acid addition salt form of amlodipine, including the besylate, prompting this court to observe that the sole active ingredient is amlodipine, and that it acts the same in the human body whether administered as a besylate salt or as a maleate salt. 359 F.3d at 1366.

Finally, there is a suggestion in Pfizer's supplemental filing with the FDA that it was known that the besylate salt of amlodipine would work for its intended purpose: "We feel that the change in salt form [from maleate to besylate] is justified since benzenesulfonate is a commercially acceptable salt, as exemplified by the tranquilizer mesoridazine (Serentil)." Thus, although Dr. Wells testified that it was not guaranteed whether amlodipine besylate would form and what its salient characteristics would be, "this does not overcome [the prior art's] teaching that [amlodipine besylate] will work." *Corkill,* 771 F.2d at 1500.

Considering all of the evidence, we conclude that the district court clearly erred in finding that Apotex failed to produce clear and convincing evidence that one skilled in the art would have had a reasonable expectation of success with the besylate salt of amlodipine.

"*Obvious-to-Try*"

To be sure, "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed.Cir.2006) (internal quotations omitted). Pfizer argues that, if anything, amlodipine in its besylate salt form would at most be "obvious to try," i.e., to vary all parameters or try each of numerous possible choices to see if a successful result was obtained. *O'Farrell*, 853 F.2d at 903.

Parties before this court often complain that holdings of obviousness were based on the impermissible "obvious to try" standard, and this court has accordingly struggled to strike a balance between the seemingly conflicting truisms that, under 35 U.S.C. § 103, "obvious to try" is not the proper standard by which to evaluate obviousness, *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A.1977), but that, under *O'Farrell* and other precedent, absolute predictability of success is not required. 853 F.2d at 903. Reconciling the two is particularly germane to a situation where, as here, a formulation must be tested by routine procedures to verify its expected properties. The question becomes then, when the skilled artisan must test, how far does that need for testing go toward supporting a conclusion of non-obviousness?

As we have said before, "[e]very case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts." *In re Jones*, 958 F.2d 347, 350 (Fed.Cir.1992). Consequently, courts cannot decide the obviousness or non-obviousness of a patent claim by proxy. Undue dependence on mechanical application of a few maxims of law, such as "obvious to try," that have no bearing on the facts certainly invites error as decisions on obviousness must be narrowly tailored to the facts of each individual case. As we stated in *DyStar*,

> Obviousness is a complicated subject requiring sophisticated analysis, and no single case lays out all facets of the legal test. [There is] danger inherent in focusing on isolated dicta rather than gleaning the law of a particular area from careful reading of the full text of a group of related precedents for all they say that is dispositive and for what they hold. When parties ... do not engage in such careful, candid, and complete legal analysis, much confusion about the law arises and, through time, can be compounded.

464 F.3d at 1367. On the facts of this case, however, we are satisfied that clear and convincing evidence shows that it would have been not merely obvious to try benzene sulphonate, but would have been indeed obvious to make amlodipine besylate.

First, this is not the case where there are "numerous parameters" to try. Rather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt. Although we recognize some degree of unpredictability of salt formation, *see, e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1379 (Fed.Cir.2006), the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious. This is especially true here, where (1) as noted above, the skilled artisan had a reasonable (although not guaranteed) expectation that amlodipine besylate would form; (2) Pfizer conceded in

prior litigation that the type of salt had no effect on the therapeutic effect of the active ingredient, amlodipine, and was practically interchangeable, *Pfizer v. Dr. Reddy's Labs.*, 359 F.3d at 1365-66; and (3) numerous other publications (described above) clearly directed the skilled artisan to a pharmaceutically-acceptable acid addition salt made from benzene sulphonate, including, significantly, the Carabateas patent which taught the besylate acid addition salt form of another dihydropyridine pharmaceutical compound.

Second, this is not the case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903; *Medichem*, 437 F.3d at 1167. Here, as admitted by Mr. Davison, in selecting an acid addition salt formulation, one skilled in the art looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry. Berge clearly pointed the skilled artisan to 53 anions that, as of 1974, were pharmaceutically acceptable. As Dr. Wells' testimony and the Carabateas patent demonstrated, one of ordinary skill in the art was capable of further narrowing that list of 53 anions to a much smaller group, including benzene sulphonate, with a reasonable expectation of success.

Finally, Pfizer protests that a conclusion that amlodipine besylate would have been obvious disregards its "discovery" because it was obtained through the use of trial and error procedures. While the pharmaceutical industry may be particularly adversely impacted by application of an "obvious to try" analysis, *see, e.g., In re Merck*, 800 F.2d at 1100 (Baldwin, J., dissenting), that Pfizer had to verify through testing the expected traits of each acid addition salt is of no consequence because it does not compel a conclusion of non-obviousness here. In coming to this conclusion, we have not ignored the fact that "[p]atentability shall not be negatived by the manner in which the invention was made."

35 U.S.C. § 103(a). Nor are we ignorant of the fact that reference to "routine testing" or "routine experimentation" is disfavored. *See, e.g., In re Yates,* 663 F.2d 1054, 1056 n. 4 (C.C.P.A.1981) ("The Solicitor ... argues that it is 'not unobvious to discover optimum or workable ranges by routine experimentation.' In many instances, this may be true. The problem, however, with such 'rules of patentability' (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue-obviousness-and exalt the formal exercise of squeezing new factual situations into preestablished pigeonholes. Additionally, the emphasis upon routine experimentation is contrary to the last sentence of section 103.") (internal citation omitted); *In re Saether,* 492 F.2d 849, 854 (C.C.P.A.1974) ("In his argument that 'mere routine experimentation' was involved in determining the optimized set of characteristics, the solicitor overlooks the last sentence of 35 U.S.C. § 103.... Here we are concerned with the question of whether the claimed invention would have been obvious at the time it was made to a person having ordinary skill in the art-not how it was achieved.") (internal citation omitted); *In re Fay,* 52 C.C.P.A. 1483, 347 F.2d 597, 602 (C.C.P.A.1965) ("[W]e do not agree that 'routine experimentation' negatives patentability. The last sentence of section 103 states that 'patentability shall not be negatived by the manner in which the invention was made.' To support the board's decision that 'routine experimentation within the teachings of the art' will defeat patentability requires a primary determination of whether or not appellants' experimentation comes within the teachings of the art. Whether the subsequent experimentation is termed 'routine' or not is of no consequence.").

However, on the *particularized facts of this case,* consideration of the "routine testing" performed by Pfizer is appropriate because the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing. *Merck,* 874 F.2d at 809. The evidence shows that, upon

making a new acid addition salt, it was routine in the art to verify the expected physicochemical characteristics of each salt, including solubility, pH, stability, hygroscopicity, and stickiness, and Pfizer's scientists used standard techniques to do so. These type of experiments used by Pfizer's scientists to *verify* the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to *discover* a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success. This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably "routine" to one of ordinary skill in the art. Rather, our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation. *Cf. Velander v. Garner*, 348 F.3d 1359, 1368 (Fed.Cir.2003) (that one skilled in the art would view variability in producing fibrinogen in transgenic mammals as evidence that "expense, time and effort" would be involved did not equate to a conclusion that success was unlikely). Simply put, to conclude that amlodipine besylate would have been obvious, "the prior art, common knowledge, or the nature of the problem, viewed through the eyes of an ordinary artisan" merely had to suggest reacting amlodipine base with benzene sulphonic acid to form the besylate acid addition salt, and that that acid addition salt form would work for its intended purpose. *DyStar*, 464 F.3d at 1361. They did. *See O'Farrell*, 853 F.2d at 904.

We find this case analogous to the optimization of a range or other variable within the claims that flows from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed.Cir.2003) (determining where in a disclosed set of percentage ranges the optimum combination of percentages lies is prima facie obvious). In *In re Aller*, 42 C.C.P.A. 824, 220 F.2d 454, 456 (1955), our predecessor court set forth the

rule that the discovery of an optimum value of a variable in a known process is usually obvious. *See also In re Boesch*, 617 F.2d 272, 276 (C.C.P.A.1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art."). Similarly, we hold that the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt. *Cf. In re Geisler*, 116 F.3d 1465, 1470 (Fed.Cir.1997) (" '[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.' " (quoting *Aller*, 220 F.2d at 456)); *In re Kulling*, 897 F.2d 1147, 1149 (Fed.Cir.1990) (finding no clear error in Board of Patent Appeals and Interferences' conclusion that the amount of eluent to be used in a washing sequence was a matter of routine optimization known in the pertinent prior art and therefore obvious). Indeed, the logical line of testing was to react benzene sulphonate with amlodipine to confirm the presence of a salt, and then to verify that the physicochemical properties of amlodipine besylate were adequate, particularly the trait of sufficient non-stickiness. The experimentation needed, then, to arrive at the subject matter claimed in the 303 patent was "nothing more than routine" application of a well-known problem-solving strategy, *Merck*, 874 F.2d at 809, and we conclude, "the work of a skilled [artisan], not of an inventor." *DyStar*, 464 F.3d at 1371; *see also In re Luck*, 476 F.2d 650, 652-53 (C.C.P.A.1973) (use of routine testing to identify optimum amounts of silane to be employed in a lamp coating, without establishing a critical upper limit or demonstrating any unexpected result, lies within the ambit of the ordinary skill in the art); *In re Esterhoy*, 58 C.C.P.A. 1116, 440 F.2d 1386, 1389 (1971) ("One skilled in the art would thus manifestly operate the Switzer et al. process under conditions most desirable for maximum and efficient concentration of the acid. The conditions recited in the claims appear to us to be only optimum and easily ascertained by routine

experimentation."); *In re Swentzel*, 42 C.C.P.A. 757, 219 F.2d 216, 219 (1955) ("It may well be that the size represents the largest particles suitable for appellant's purpose, but the determination of that desired size under the present circumstances involves nothing more than routine experimentation and exercise of the judgment of one skilled in the art."); *In re Swain*, 33 C.C.P.A. 1266, 156 F.2d 246, 247-48 (1946) ("In the absence of a proper showing of an unexpected and superior result over the disclosure of the prior art, no invention is involved in a result obtained by experimentation.").

Thus, while patentability of an invention is not negated by the manner in which it was made, "the converse is equally true: patentability is not imparted where 'the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success.' " *Merck*, 874 F.2d at 809 (quoting *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed.Cir.1988)). For these reasons, we hold that Apotex introduced clear and convincing evidence that a skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine at the time the invention was made. Accordingly, we agree with the district court that a prima facie case of obviousness was established with regard to the claims of the 303 patent, albeit for different reasons.

Secondary Considerations

Before we turn to the remaining conflict between the parties-the district court's consideration of the objective indicia of non-obviousness-we must first address the district court's reference in its bench opinion to Pfizer's business decision to switch its commercial product from an amlodipine maleate formulation to an amlodipine besylate formulation, apparently as evidence of non-obviousness. *See Bench Order Tr.* at 6:21-7:1 ("Pfizer is a big company,

which by this time had a large investment in amlodipine maleate.... A decision to switch to some other product, or even to abandon the entire product, is the corporate equivalent of turning the Queen Mary."); *Bench Order Tr.* at 18:17-21 ("Pfizer would not have changed from the maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason."). The district court's reliance on this "objective consideration" seems suspect as there is no evidence in the appellate record to support the implicit finding that Pfizer ever considered abandoning amlodipine or stood to lose significant time and investment dollars. Indeed, we are not ignorant of the fact that pharmaceutical companies are in the business of research and development. We therefore disregard the district court's findings on this point as clearly erroneous, or in any event insufficiently probative of non-obviousness to overcome the evidence of the prior art teachings.

Evidence of unexpected results can be used to rebut a prima facie case of obviousness. *Peterson*, 315 F.3d at 1330. The district court found that, while amlodipine besylate was not superior to amlodipine maleate in every category of physicochemical properties, it nonetheless "clearly and unexpectedly illustrates a superior combination of properties when compared to" amlodipine maleate.[6] With regard to solubility, the 303 patent discloses that amlodipine besylate has a solubility of 4.6 mg/ml at pH 6.6, whereas amlodipine maleate has a solubility of 4.5 mg/ml at pH 4.8. The district court stated that any product having a solubility greater than 1.0 mg/ml is acceptable, and that "[t]he rest is sound and fury." *Bench Order Tr.* at 11:10. We conclude from this

[6] We reject Apotex's assertion that the district court erred by giving weight to the commercial success of Norvasc®. The district court relied on the production of billions of amlodipine besylate tablets by Pfizer as evidence of non-stickiness rather than commercial success. Apotex's arguments with regard to an alleged absence of a "nexus" between the claimed features and the sales of Norvasc® are therefore irrelevant.

statement that the district court did not find that the solubility of amlodipine besylate was materially superior, much less "unexpectedly superior" to the solubility of amlodipine maleate. Similarly, we also conclude that the district court did not rely on non-hygroscopicity as a secondary consideration. Thus, the two allegedly unexpected and superior properties remaining are drug stability and tablet processing.

With respect to stability, the district court found that the 303 patent provided an ordinal listing of several tested salts descending in rank order from the most stable to the least stable, where the besylate salt was the most stable of the eight salts tested, and the maleate salt was the sixth most stable salt. The district court also found that amlodipine besylate was "sufficiently nonsticky to obtain commercial processability." Pfizer asserts that these improvements have significant practical value and are indicative of non-obviousness.

In contrast, Apotex asserts that the district court committed several errors when assessing secondary considerations. Specifically, Apotex asserts that the district court erred by comparing amlodipine besylate only to the maleate preferred embodiment disclosed in the 909 patent rather than the entire genus of amlodipine salts claimed therein. Apotex also asks this court to discount Pfizer's evidence of unexpectedly superior properties because the stability and drug processing properties of amlodipine besylate are neither "unexpected" nor "surprising." Finally, Apotex asserts that even if amlodipine besylate exhibits a better combination of solubility, pH, stability, non-hygroscopicity, and non-stickiness properties than other members of the genus of amlodipine salts, this purported superiority of amlodipine besylate is not significant enough as a matter of law to make it non-obvious. Apotex argues that amlodipine is the active ingredient and the sole source of therapeutic effects of amlodipine besylate, whereas the besylate is merely a means of delivering the amlodipine part

of the molecule. Thus, Apotex asserts, any salt need only exhibit *adequate* physicochemical characteristics in order to serve its purpose of delivering the amlodipine. Apotex contends that the record here demonstrates that the amlodipine maleate tablet also performs these same functions. The issue before us is whether, based upon the evidence as a whole, Pfizer's showing of superior results was sufficiently unexpected so as to rebut Apotex's showing of a prima facie case of obviousness.

While we agree that the teaching of a prior art patent is not limited to its preferred embodiment, *see Merck,* 874 F.2d at 807 ("the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered"), the other amlodipine salts of which Apotex complains (i.e., amlodipine tosylate and amlodipine mesylate) were not expressly recited in the 909 patent or elsewhere in the prior art. Thus, the district court's obligation to consider the entire range of prior art compounds would have been satisfied here by its comparison of the closest prior art compound to amlodipine besylate. *Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 970 (Fed.Cir.2006) (" '[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.' ") (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed.Cir.1991)). However, there is precious little (if any) evidence to support any implicit finding by the district court that amlodipine maleate is actually the closest prior art compound to amlodipine besylate. Indeed, the prior art of Schmidt, Spiegel, Carabateas, and Barth, discussed above, evidences that one skilled in the art would expect an acid addition salt made from benzene sulphonate to have good physicochemical properties.

Another defect in the district court's reasoning is its failure to recognize that by definition, any superior property must be *unexpected* to be considered as evidence of non-

obviousness. *In re Chupp*, 816 F.2d 643, 646 (Fed.Cir.1987). Thus, in order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected. *Merck*, 874 F.2d at 808. Here, Pfizer's evidence must fail because the record is devoid of *any* evidence of what the skilled artisan would have expected. We will not simply presume that the skilled artisan would have expected that amlodipine besylate would have the same characteristics as amlodipine maleate, because as Pfizer asserts, its properties are not absolutely predictable. Further, Dr. Wells' testimony reflects the fact that he believed that amlodipine besylate would solve the problems of amlodipine maleate. Unrebutted testimony from Apotex's expert evidences that, given the range of 53 anions disclosed by Berge, one skilled in the art would expect those anions to provide salts having a range of properties, some of which would be superior, and some of which would be inferior, to amlodipine maleate. Pfizer has simply failed to prove that the results are unexpected. *Boesch*, 617 F.2d at 278.

Finally, we do not see the trial court's finding that amlodipine besylate had *adequate* physicochemical characteristics as sufficient to uphold the court's ultimate holding of unexpected superiority. Pfizer rejected amlodipine maleate not because it failed to exhibit an adequate combination of solubility, pH, stability in capsule form, and non-hygroscopicity, but because it could not be easily manufactured because of stickiness and limited stability of amlodipine maleate in the preferred commercial form of a tablet. The district court wrongly relied on the fact that the "besylate salt works" because considerable evidence shows that amlodipine maleate also worked for its intended purpose and even did so in human clinical trials, even though somewhat inferior in ease of tableting and projected shelf-life. At most, then, Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine. Creating a "product or

process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient ... to enhance commercial opportunities ... is universal-and even common-sensical." *DyStar*, 464 F.3d at 1368. Amlodipine besylate is obvious on the facts of this case because the 909 patent suggested-and Dr. Wells expected-that every other potential salt form of amlodipine would be adequate for its intended purpose, i.e., to increase bioavailability of amlodipine, and would solve the stickiness problem of the maleate salt. The fact that amlodipine besylate was the best of the seven acid addition salts *actually tested* proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art. *See Aller*, 220 F.2d at 456 ("[E]ven though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art."). These facts lead us to conclude that the resulting commercial embodiment claimed in the 303 patent, amlodipine besylate, does not satisfy the standards of patentability.

Alternatively, we hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed.Cir.1988). Here, the record establishes such a strong case of obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient. *Id.* at 769.

From our de novo assessment of the determination below on obviousness in view of all of the evidence and for the reasons articulated above, we conclude that the district court erred in holding that the claims of the 303 patent would not have been obvious.

III. CONCLUSION

Because we find claims 1-3 of the 303 patent invalid for obviousness, we find it unnecessary to address Apotex's assertion that Pfizer engaged in inequitable conduct during prosecution of the 303 patent and that its patent should therefore be declared unenforceable. For the aforementioned reasons, the district court's judgment is reversed.

REVERSED.

LINN, Circuit Judge, concurs in the result.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2006-1261

PFIZER, INC.,
Plaintiff-Appellee,

v.

APOTEX, INC. (formerly known as TorPharm, Inc.)
Defendant-Appellant.

Before MICHEL, Chief Judge, NEWMAN, MAYER, LOURIE, RADER, SCHALL, BRYSON, GAJARSA, LINN, DYK, PROST, and MOORE, Circuit Judges.

ORDER

The Appellee, Pfizer, Inc. filed a combined petition for panel rehearing and rehearing en banc, and a response thereto was invited by the court and filed by the Appellant, Apotex, Inc. The petition for rehearing was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response were referred to the circuit judges who are authorized to request a poll whether to rehear the appeal en banc. A poll was requested, taken, and failed.

Apotex, Inc. moves for expedited denial of rehearing and rehearing en banc, and for expedited issuance of the mandate. Pfizer, Inc. opposes.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The petition for rehearing and rehearing en banc is denied.

(2) The motion for expedited denial of rehearing and rehearing en banc is denied as moot.

(3) The motion for expedited issuance of the mandate is granted.

NEWMAN, LOURIE, and RADER, Circuit Judges, would rehear the appeal en banc.

NEWMAN, Circuit Judge, dissents in the denial of the petition for rehearing en banc in a separate opinion.

LOURIE, Circuit Judge, dissents in the denial of the petition for rehearing en banc in a separate opinion.

RADER, Circuit Judge, dissents in the denial of the petition for rehearing en banc in a separate opinion.

FOR THE COURT

May 21, 2007
Date

s/ Jan Horbaly
Jan Horbaly
Clerk

ISSUED AS A MANDATE: MAY 21, 2007

NEWMAN, Circuit Judge, dissenting from the denial of rehearing *en banc*.

The court has not accepted the suggestion that this case be reviewed *en banc*, and the panel was unpersuaded by the argument that the decision is incorrect when the law of precedent is applied. I write separately because the panel's statement of the applicable law and its application to the facts of this case are inconsistent with the court's precedent. Our obligation as an appellate court is to assure that the law is both correctly stated and correctly applied. When inconsistency is raised by the panel's treatment, our obligation is to assure that conflicts with precedent -- whether real or apparent -- are resolved, as well as to assure that the law is correctly applied. From the court's denial of rehearing *en banc*, I respectfully dissent.

The ruling in this case has important policy as well as legal implications, as the many amici curiae point out, each side stressing a different aspect of the effect on commercial activity in the pharmaceutical field. Both sides acknowledge that the effects of chemical changes on properties of medicinal products is not predictable; the difference residing in the panel's acceptance of the long-discredited "obvious to try" standard, on which the panel superimposes the theory that the skill of these inventors guided them to trial of the besylate salt (despite the prior art's preference for the maleate salt), thereby negating patentability. The panel's application of the obvious-to-try standard is in direct conflict with precedent; it has long been the law that "patentability shall not be negated by the manner in which the invention is made." 35 U.S.C. § 103. In *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990) this court stated that "we have consistently held that 'obvious to try' is not to be equated with obviousness." In *In re Tomlinson*, 363 F.2d 928, 931 (CCPA 1966) the court explained that "there is usually an element of 'obviousness to try' in any research endeavor, that . . . is not undertaken with complete blindness but rather with some semblance of a chance of success." The

amici curiae representing research pharmaceutical industries in this petition point out that methodical experimentation is fundamental to scientific advance, and particularly for biological and medicinal products, where small change can produce large differences. At the trial there was no contradiction to the testimony of Pfizer's expert witness Dr. Anderson that "one of ordinary skill in the art could neither draw any conclusions nor have any expectations about the properties of amlodipine besylate from the properties of a besylate salt of a different compound." Pfizer Br. at 7. Indeed, the parties stipulated this scientific fact.

Nor was there any evidence contradicting Pfizer's position that "the superior properties at issue were not some abstract concept of 'good' properties, but specific properties which solved both the sticking and instability problems of the prior art, while providing non-hygroscopicity and good solubility. . . . Trade-offs in salt properties are the rule, and one of skill must usually accept some undesirable properties to achieve other desirable ones. Amlodipine besylate, unlike any other amlodipine salt, presented no trade-offs." *Id.* The panel further erred in declining to give weight to these acknowledged "secondary considerations" of unexpected results. *See Richardson-Vicks, Inc. v. Upjohn Co.*,122 F.3d 1483 (Fed. Cir. 1997) (evidence of unexpected results must be considered); *Ruiz v. AB Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000) ("Our precedents clearly hold that secondary considerations, when present, must be considered in determining obviousness.")

The panel decision changes the criteria as well as the analysis of patentability, with results of particular significance for their effect on the conduct of R&D, the costs of drug development, and the balance between generic access to established products and the incentive to development of new products. The amici curiae on both sides of the issue stress different policy considerations: the pharmaceutical research companies point out that diminished access to patenting will affect the kind and direction of product

development; the generic producers point out that the sooner they can enter the market for established drugs, the lower the consumer price. The placement of the balance in this ever-present conflict between innovator and copier has long engaged the public and Congress, and needs must continue to do so. Meanwhile, however, it is inappropriate for a panel of this court to make a change in the precedent by which both sides of the debate have heretofore been bound.

Stability of precedent and the uniform application of correct law to achieve the correct result are the assignment of the Federal Circuit, for our rulings are of nation-wide effect. A primary purpose for which our court was formed was to provide the judicial stability that supports commercial investment -- this was a unique judicial role, and was adopted in recognition of the dependence of technology-based industry on an effective patent system. It was recognized that a nationally uniform, consistent, and correct patent law is an essential foundation of technological innovation, which is today the dominant contributor to the nation's economy. *See the Report of the Domestic Policy Review of Industrial Innovation*, Department of Commerce 1979 (stressing the need for judicial administration of correct and uniform patent law). In enacting the implementing statute, Congress explained:

> The purpose [of establishment of the Federal Circuit] is to resolve some of the myriad structural administrative and procedural problems that have impaired the ability of our Federal courts to deal with the vast range of controversies among our citizens and to respond promptly and meaningfully to their demands for justice . . . which include the inability of our present system to provide a prompt, definitive answer to legal questions of nationwide significance . . .

S. Comm. on the Judiciary, Federal Courts Improvement Act of 1981, S. Rep. No. 97-275, at 1 (1981).

When conflicts arise between panel decisions of the Federal Circuit the ensuing uncertainty is of national scope, contravening the purpose of establishing this court. This adds weight to our obligation to undertake *en banc* review, both to reestablish consistency in the law and to correct errors in panel decisions. In 1998, in a letter to the Commission on Structural Alternatives for the Federal Courts of Appeals, Justice Scalia wrote:

> [T]he function of en banc hearings . . . is not only to eliminate intra-circuit conflicts, but also to correct and deter panel opinions that are pretty clearly wrong . . . . The disproportionate segment of [the Supreme Court's] discretionary docket that is consistently devoted to reviewing [a regional court of appeals'] judgments, and to reversing them by lop-sided margins, suggests that this error-reduction function is not being performed effectively.

Letter dated Aug. 21, 1998, *Hearing before the S. Subcomm. on Administrative Oversight and the Courts of the S. Comm. on the Judiciary*, 106th Cong. 72 (1999).

Justice O'Connor wrote in similar vein:

> It is important to the federal system as a whole that the Courts of Appeals utilize en banc review to correct panel errors within the circuit that are likely to otherwise come before the Supreme Court.

Letter dated June 23, 1998, id. at 71.

For the Federal Circuit, it was intended and expected that this court would provide uniform national law in all of the fields assigned to our exclusive jurisdiction; not only in patent law. Our cases are rarely factually simple, and when there arise apparently divergent panel statements of the law and its application, the responsibility for en banc review

looms large. The goal of judging is "full, equal and exact" enforcement of the law. *See* Roscoe Pound, "The Etiquette of Justice," 3 Proceedings Neb. St. Bar Assn. 231 (1909) ("full, equal and exact enforcement of substantive law is the end" of the judicial process). Through the system of en banc review, courts can remedy panel lapses, if indeed this decision represents such a lapse, or uniformly adopt panel advances in the law, if indeed this decision represents such an advance. From the court's decision to decline this review, I must, respectfully, dissent.

LOURIE, Circuit Judge, dissenting from the denial of rehearing en banc.

I respectfully dissent from the court's decision not to rehear this case en banc. At bottom, I consider that the decision of the panel was incorrect. But, we do not rehear appeals simply because a non-panel member disagrees with its result. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1043 (Fed. Cir. 2006) (Lourie, J., concurring) ("I do not believe that every error by a panel is enbancable. A panel is entitled to err without the full court descending upon it."). Federal Rule of Appellate Procedure 35(a) provides that "[a]n en banc hearing or rehearing is not favored and ordinarily will not be ordered unless: (1) en banc consideration is necessary to secure or maintain uniformity of the court's decisions; or (2) the proceeding involves a question of exceptional importance." Our Internal Operating Procedures ("IOPs") state that "[a]mong the reasons for en banc actions are: (1) necessity of securing or maintaining uniformity of decision; (2) involvement of a question of exceptional importance; (3) necessity of overruling a prior holding of this or a predecessor court expressed in an opinion having precedential status; or (4) the initiation, continuation, or resolution of a conflict with another circuit." IOP 13(2).

However, consistent with those established criteria for taking a case en banc, I consider that the panel erred in its legal determinations, and that those errors will confuse the law relating to rebuttal of a prima facie case of obviousness of a chemical compound. Thus, an en banc hearing is warranted in this case in order to maintain uniformity of the court's decisions and because it presents questions of exceptional importance.

The panel reversed the district court's decision that claims relating to amlodipine besylate (the active ingredient in the hypertension drug Norvasc®) were valid and nonobvious after a bench trial. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). In my view, several legal

errors were made in this decision, and improper deference was given to fact-findings of the district court.

First, the panel failed to defer to fact-findings made by the district court that were not clearly erroneous regarding the unexpected properties of amlodipine besylate. Evidence in the record, including trial testimony of experts and Pfizer scientists, internal research and development documents, and a scientific article, supported the district court's finding that "the besylate salt clearly and unexpectedly exhibited a superior combination of properties when compared to what was suggested in the preferred preparation." *District Court Oral Op. Tr.* at 23:13-15; *see* Pet. for Reh'g en banc at 5-6. The panel disregarded that express finding of fact, holding that "Pfizer has simply failed to prove that the results are unexpected." *Pfizer*, 480 F.3d at 1371. Moreover, relying on the testimony of both parties' experts, the district court found that there was no reasonable expectation of success with regard to using the besylate salt form of amlodipine. *District Court Oral Op. Tr.* at 23:1-9. However, rather than give deference to the district court's fact-findings, the panel substituted its own finding that a reasonable expectation of success existed in the art. *See Pfizer*, 480 F.3d at 1361, 1364-65 ("The record also satisfies us that, contrary to the district court's finding, a reasonable fact-finder could only conclude that the skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine."). Much public discussion has occurred, and even judicial comments in opinions, that we should defer to district court judges concerning certain aspects of claim construction, which we have held is a matter of law. Be that as it may, it is undisputed that we must defer to fact-findings by a district court, unless they are clearly erroneous, and I do not believe that they were here.

In addition, the panel improperly placed greater importance on the therapeutic value of a claimed compound over the value of its physical properties. The panel concluded that the improvement of the invention, which related to drug

formulation, viz., increased stability and decreased stickiness, was "insufficient" to meet the standards of patentability. *Id.* at 1368 (emphases added) ("[W]e hold that the *optimization of the acid addition salt formulation* for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation *has no effect on the therapeutic effectiveness* of the active ingredient and the prior art heavily suggests the particular anion used to form the salt."). I read that conclusion as improperly requiring a compound to possess a specific type of improvement over the prior art—in this case, improved therapeutic properties—to be patentable, negating other important properties, a conclusion that is not compelled by our case law and not sound. Any useful and unexpected property should be eligible to overcome a prima facie obviousness determination. *See In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. . . . There is no basis in law for ignoring any property in making such a comparison.").

Third, the panel also found that the invention was the result of routine experimentation, and therefore was not patentable. *See Pfizer*, 480 F.3d at 1367 (emphases added) (stating that the "type of experiments used by Pfizer's scientists to *verify* the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to *discover* a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success"). That conclusion conflicts with the statutory requirement that "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103(a). Moreover, the conclusion contradicts the district court's supported findings that the results were unexpected, and that the experiments led to showing the totality of the properties of the invention, *see Papesch*, 315 F.2d 381, which makes the compound nonobvious, not merely to the *verification* of results.

In addition, holding an inventor's expectations of success against the objective unexpectedness of the properties of the compound unfairly suggests that an inventor should try only that which he doubts will work. *See Pfizer*, 480 F.3d at 1371 ("Dr. Wells' testimony reflects the fact that he believed that amlodipine besylate would solve the problems of amlodipine maleate."). Inventors generally are optimistic about what they choose to experiment with, but that does not necessarily suggest obviousness.

These issues are of exceptional importance. Chemical and pharmaceutical compounds often can be found to be prima facie obvious, as they are based on prior work that could reasonably suggest them, *see KSR Int'l Co. v. Teleflex Inc.*, --- S.Ct. ---, 2007 WL 1237837 (Apr. 30, 2007), but commercialization of such compounds may depend on their possession of unexpected properties. Such properties may be biological or physical. A failure to recognize all such properties that may be relevant to the value of such a compound may doom the compound to being poured down the drain rather than becoming an important therapeutic. The general public, innovative companies, and, ultimately, generic companies, depend upon faithful adherence to this principle. In addition, our cases hold that unexpected properties make for non-obviousness, *see Papesch*, 315 F.2d 381, and this decision disdains such properties if they are not biological. That is a conflict with our precedent that needs resolution.

Not least, the question of deference to district courts, at least on fact issues, needs reaffirming. We must not shy away from reversing fact-findings that truly are clearly erroneous, as we do encounter them from time to time, but this case does not present them.

Thus, I would rehear this case, and I dissent from the court's determination not to do so.

RADER, Circuit Judge, dissenting from the denial of rehearing *en banc*.

I respectfully dissent from the decision to deny rehearing.

In this case, the trial court made the factual determination that the besylate salt form of amlodipine had unexpected superior properties over the closest prior art. Accordingly, the underlying patent ('303) was valid and nonobvious. Three separate district courts held trials involving the '303 patent. Indeed, each of those three different district court judges came to the same factual conclusion regarding the nonobviousness of amlodipine besylate. Because the factual determinations in the case below were not clearly erroneous, this court should have deferred to the district court's factual findings.

As the testimony indicated, the properties of new pharmaceutical salt forms are entirely unpredictable. Even the Berge reference on which the panel relied clearly states: "Unfortunately there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." The district court agreed and made the factual determination that the superior properties of amlodipine besylate over the prior art (increased stability and decreased stickiness) were indeed unexpected – a finding that deserved deference.

Furthermore 'obvious to try' jurisprudence has a very limited application in cases of this nature. With unpredictable pharmaceutical inventions, this court more wisely employs a reasonable expectation of success analysis. In this case, salt selection is unpredictable, thus rebutting, as most other courts found, any reasonable expectation of success. Although the panel gives "lip service" to the principle that 'obvious to try' does not work in this field, it nonetheless appears to be the basis for its decision in this case. In addition, the panel discerned a reasonable expectation of success by giving

undue emphasis to the inventor's subjective hopes for the outcome of his experiments.

The panel also mistakenly determined that the superior properties of the besylate did not overcome a prima facie case of obviousness because they showed no superior therapeutic value—the maleate salt form of amlodipine worked just as well as the besylate form in clinical trials. Therapeutic value, however, is just one property of a pharmaceutical. Other properties, such as solubility, stability, hygroscopicity, and processability, must also play a role in the analysis of advantages. The superior properties of the besylate salt form of amlodipine, overcame the stability and stickiness problems that existed with the maleate salt form and created a superior formulation. Although the maleate salt form was also therapeutically effective, the besylate form was still a significant improvement because it overcame the stability and processing problems that could have prevented successful commercial marketing.

The panel also found that amlodipine besylate was not patentable since it was made by a routine testing or a "well known problem solving strategy." This clearly violates the statutory mandate that "patentability shall not be negatived by manner in which the invention was made." 35 U.S.C. § 103(a). Many if not most pharmaceutical inventions are discovered through a routine screening protocol or through an established trial and error process. Pharmaceutical inventions discovered by these routine screening methods include not only new formulations and salt forms, but also include the active pharmaceutical compounds themselves. Thus, this decision calls into question countless pharmaceutical patents, which in turn could have a profoundly negative effect on investments into the design and development of new life-saving pharmaceuticals. With many questions about this case, I would have reheard it en banc.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS

3-C-5289 (JMR/MTM)

PFIZER, INCORPORATED,
Plaintiff,

-v-

APOTEX, INCORPORATED,
Defendant.

BENCH ORDER: January 17, 2006

BEFORE CHIEF JUDGE JAMES M. ROSENBAUM (Of the District of Minnesota) Chicago, Illinois

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In the matter of Pfizer, Incorporated versus Apotex, Incorporated, this is an action for patent infringement under the Hatch-Waxman Act, at 21 U.S.C. Section 355 J, and 35 U.S.C. Section 271(e)(2). Congress apparently enacted Hatch-Waxman to expedite the delivery of pharmaceuticals to the consuming public. Plaintiff, Pfizer, Incorporated, makes, and it holds a patent on a commercial drug product called Norvasc, an extremely successful drug. The drug is primarily used to treat high blood pressure angina. Norvasc is covered by two patents, number 4,572,909, that's the '909 patent, and 4,872,303, the '303 patent. Defendant, Apotex, Incorporated, has filed an Abbreviated New Drug Application, indicating its intent to produce a generic drug product which will be the chemical equivalent to the invention claimed in the '303 patent.

Pfizer asserts that the defendant's application is an act

of infringement and seeks an injunction barring Apotex from producing its product until the expiration of the protection afforded by the '303 patent. Apotex has replied by challenging the validity of the '303 patent. This challenge is the gravamen of this lawsuit.

The Court announces its decision pursuant to Rule 52 of the Federal Rules of Civil Procedure, which provides in part, that "in all actions tried upon the facts without a jury, the Court shall find the facts specifically and state separately its conclusions of law thereon. It will be sufficient if the findings of fact and conclusions of law are stated orally and recorded in open court following the close of the evidence." There are internal ellipses within that quote.

The Court begins by adopting and incorporating the parties' excellent stipulation of uncontested facts. Having done so, it will be apparent that there are very few contested facts in this case. The parties vigorously contest the upshot of many of the facts and events which have occurred here, but with very few exceptions they agree as to the actual occurrences.

Norvasc's active ingredient is amlodipine, a chemical compound isolated as a chemical base. Amlodipine is in fact the invention which is the subject of the '909 patent. It is frequently the case, then, in order to make a pharmaceutical drug from a chemical base, it is necessary to combine the base with a chemical acid to create a chemical salt. This very common event is also described in the '909 patent. An ideal pharmaceutical salt is stable, soluble, pure, and able to be processed in marketable dosage form.

Pfizer's '909 patent claimed not only the active amlodipine ingredient, but also a pharmaceutically acceptable acid addition salt containing amlodipine. Within its text, the patent alludes to no fewer than a dozen possible amlodipine salts. The '909 patent specifically identifies amlodipine maleate as the preferred salt form. Having identified --

having invented amlodipine and obtaining its patent, Pfizer undertook to develop it for commercial sale. The path proved rocky.

When it began to prepare amlodipine maleate for commercial distribution, two major problems developed. During testing, the maleate salt revealed, first, chemical *instability; second, when Pfizer's product was being tested* for production in the tablet form, a form all parties agree is the most desirable and the most desired by consumers, the blend of amlodipine maleate showed a tendency to stick or film on the tablet-making machinery. This made it difficult to produce a fast, economical tablet and seriously complicated the ability to mass produce reliable dosage amounts. The problems were so great, that even after isolating an efficacious product and protecting it by an issued patent, Pfizer seriously considered abandoning commercial development of the product. Pfizer had a drug which could help the public, but they couldn't get it to needful patients.

This was no small problem, as acknowledged by Apotex's expert, Dr. Michael Cima. Pfizer is a big company, which by this time had a large investment in amlodipine maleate. It was well on its way to commercial distribution. A decision to switch to some other product, or even to abandon the entire project, is the corporate equivalent of turning the Queen Mary.

Pfizer's research team in Sandwich, England, returned to their laboratory benches, seeking new salts which might possess the desired chemical stability and tablet-making properties. Pfizer employees, Dr. James Wells and Edward Davison, tested various salt forms for several properties: Solubility, stability, nonhygroscopicity, and processability or stickiness.

As is typical in chemical laboratory work, their lab notes were recorded in laboratory notebooks. Testimony revealed that Pfizer had a procedure under which it issues

these notebooks, apparently dated and numbered. They are kept and maintained by the company as research and business records.

Doctors Wells and Davison also described an informal, and today somewhat problematic, informal set of laboratory notebooks which they themselves adopted. These were not the Pfizer-issued books, but were apparently obtained and maintained in a less formal fashion by this team. These notebooks were apparently kept in laboratory drawers, identified by the researcher's initials, and dated.

Of interest in this case, it now appears some 20 years after the facts, that certain of these notebooks, including some of their original records of test results, have been lost.

The Court finds, first, that these notebooks did exist.

Their existence is independently confirmed by allusion to some of their recorded experiments in Pfizer's regularly issued and maintained laboratory notebooks. Here the Court makes an explicit finding: Apotex claims the absence of the internally maintained -- informally maintained laboratory notebooks is, de facto, spoliation. It claims the absence of these documents is a smoking gun, aimed at the heart of the research supporting the '303 patent. The Court rejects this position. The '303 patent was issued in 1987. The informal laboratory notebooks were necessarily authored and utilized prior to that time. Both Dr. Wells and Davison have long departed from Pfizer, and the amlodipine team has scattered to the winds. It is not at all inconceivable to the Court, that when these out-of-the-ordinary notebooks were found by some impossible to identify Pfizer employee, they were simply tossed. The patent was ages old, as patents go. Certainly it would be more desirable to have these documents, but two decades after the events, the Court cannot find their absence to be evidence of skullduggery. There is absolutely no evidence, beyond their absence, that

these unavailable notebooks contained any damaging or indeed supportive material for either side.

Turning away, then, from what even a color-blind judge considers a red herring, and back to the real issues at hand, the research team hit upon the use of benzene sulphonate as one of the acids which could produce an acceptable salt in combination with the amlodipine base.

This was no small task. As will be discussed below, many organic acids will not do so. Some will only form oils, some are unstable, some produce undesirable or dangerous byproducts. The addition of the benzene sulphonate turned amlodipine into a besylate salt. This was the Pfizer team's discovery, of which a good deal more later. But it is this compound, amlodipine besylate, which is the subject of the now-challenged patent. Pfizer applied for what is now the '303 patent. Cited as relevant references for the '303 patent was Pfizer's '909 patent, U.S. patent number, numbers 3,816,612, and 4,032,637, and a scholarly article, Pharmaceutical Salts, which will be referred to as the Berge Article, authored by Stephen Berge, et al. And that is in Pharmaceutical Salts, 66 Pharmaceutical Sciences 1, January 1977.

Pfizer claimed the amlodipine besylate displayed the most desirable set of properties to produce a commercial amlodipine product for market. These included good solubility, stability, nonhygroscopicity, and processability.

In specific, Table 1 of the '303 patent details solubility. It gives solubility values for amlodipine besylate, amlodipine maleate, and several other salts. The patent is clear: A salt with a solubility factor greater than 1.0 milligrams per milliliter is desirable. This solubility permits the production of a commercial product, which must be mixed with diluents, carriers, and pharmaceutically inactive products in order to make a dispensable tablet or injectable dosage. This solubility, in particular, allows sufficiently

large amounts of active ingredient, here amlodipine, to be given to the patient in a pill, which is convenient for administration. Greater solubilities aid in the formulation of parenterel, that is injected, dosage forms of the drug.

Table 1 lists aqueous solubility of amlodipine besylate at 4.6 and amlodipine maleate at 4.5. This figure was much challenged at trial, and may not be accurate.

Evidence was offered to suggest it was inaccurate, it was mistaken, it was faked, or it was accurate and varied from batch to batch, or experiment to experiment. It may even have been a figure mistakenly transposed from other results, mixed up with an analysis of saline solutions. Other uncontested evidence suggested it may have varied as a result of greater or lesser skill in manufacture or in varying purities of the amlodipine being analyzed. The Court considers there is good evidence showing that amlodipine besylate actually demonstrates a solubility of 3.5 milligrams per milliliter in an aqueous solution, at JTX 9, at 3, and 4.6 in a saline solution, PTX 90.

Notwithstanding Apotex's zealous urging, the Court does not find this challenged number, even if it is off slightly, to amount to a hill of beans. The question for a drug company seeking to produce a drug product for tablet and injection administration is whether the product has a solubility which exceeds 1.0 milligrams per milliliter. Amlodipine besylate does so. The rest is sound and fury, signifying nothing. Any misstatement there is, and the Court does not consider it so, is immaterial.

The '303 patent next ranks stability. It provides a table in column 3 of the patent listing several tested salts. This table shows the besylate salt to be the most stable of eight salts listed. The maleate salt is sixth on the list. This table is purely ordinal. It just orders the chemicals by stability, most stable to least, without giving solubility

values. It merely bears a set of arrows descending in a stability rank ordering.

The patent identifies hygroscopicity. The tendency of a salt to take on water as another issue. Here, the Court recognizes that a chemical can take on water in more than one way: It can simply attract water to its surface, water can be incorporated as part of its molecule or into its crystalline structure, in both predictable and unpredictable fashions. And water, when taken into or onto a molecule can either be inactive, or it can have that water enter into chemical reactions with the salt, which can be highly undesirable in pharmaceuticals.

Pharm -- Apotex's experts suggest that amlodipine besylate is actually hygroscopic, which renders its claim that it is not hygroscopic false. The Court rejects their testimony on this point. In the Court's view, their testimony is accurate only in the most hyper technical sense, and not as applied to the facts of this case. The base problem of the case, and the ultimate problem with amlodipine maleate, the subject of the '909 patent, is that along with its stickiness, it is subject to chemical changes when exposed to water. When exposed to water, it undergoes the Michael Addition reaction, creating at least ten degradation products, making it unsuitable for medical purposes.

Defendant's experts suggest that amlodipine besylate is hygroscopic for three reasons: First, apparently, because it precipitated from an aqueous solution, the product can exist as a hydrate; second, because it may have water within its crystalline structure; and third, because it can have water on its surface and at extended temperatures and humidities. All three of these facts are true. Each is entirely unenlightening. The reason is simple: Everyone recognizes that the major problem, indeed the dangerous problem, with the maleate salt, is its susceptibility to the Michael Addition reaction.

Amlodipine besylate does not manufacture -- manifest this dangerous and pharmaceutically disqualifying tendency. In this regard, and fairly considered, the Court finds that in the context of this case, Pfizer's patented product is not hygroscopic, and its patent claims to that effect are entirely true.

The '303 patent's final listed factor is processability, or stickiness. Pfizer measured for stickiness by running numbers of tablets and measuring the amount of product sticking in the punch face after each run. Obviously, a number of different techniques were used. The patent states that tablets were produced in runs of 50, 100, 150, 250, and 300 -- if I left out 200, that's fair too -- during the course of the testing. While no documentary evidence was produced which showed that those tests were conducted, evidence was certainly adduced based upon the work conducted by Ms. Teresa Cutt, showing extensive runs of tablets resulting in tens of thousands of tablets of amlodipine besylate. Here I reference JTX 10, Figure 8; PTX 86, Figure 10; PTX 88, and -- at Figure 1. Internal memos show testing after 150 tablets for all of the salts listed in the patent, JTX 9. There do not appear to be rigorous tests for stickiness in these cases, although it appears that the processing runs worked. These larger production runs were not cited in the '303 patent. Under any circumstance, however, the Court finds that extensive testing was done, and it was shown, first, that the amlodipine besylate was sufficiently nonsticky to obtain commercial processability, and whether or not there are exact documents supporting it, I do not find they are a false declaration in any sense.

So, I focus then on the ultimate question, and that is the validity of the '303 patent. I begin with the essential understanding of the burden which is borne by a party who wishes to invalidate an issued patent. The party which challenges a patent has the burden of showing invalidity by clear and convincing evidence. This burden, of course, is noted in countless cases, but for the purposesof this opinion, I

cite *Kaufman vs. Lantech* at 807 F.2d 970 at 973, Fed. Cir. 1986. And the reason for this burden is because in order to have a stable patent system, an issued patent enjoys a presumption of validity and regularity, unless the challenger shows substantial evidence that something was seriously wrong.

In this case, Apotex advances three theories to support its claim that Pfizer's '303 patent is invalid. They claim, first, the '909 patent anticipates the '303; second, the '303 patent is invalid for obviousness; and third, plaintiff engaged in inequitable conduct before the Patent Office. If Apotex is able to prove any of these theories by clear and convincing evidence, its challenge would be successful and the '303 patent would be found invalid. The Court determines as a matter of fact and law, that Apotex has failed to sustain its burden.

Directing its attention to anticipation, I note that 35 U.S.C. Section 102(a) provides that an invention must be novel to merit a patent. A patent is not novel if it is anticipated or described in a printed publication, in this or a foreign country. An invention is anticipated if every element or limitation found in the patent claims can be found in a single prior art reference. Here I refer to *Scripps Clinic & Research* at 927 F.2d 1565 at 1576, Fed. Cir. 1991. Apotex asks the Court to find the '909 patent anticipates the '303 patent.

The defendant argues that the '909 patent claims amlodipine and amlodipine mixed with one of a class of salts of which besylate is a member. According to Apotex, the '909 patent claims a limited genus of amlodipine salts of which amlodipine besylate is a species. From this assertion, they claim that the '909 patent anticipates the '303. In general, these areas are discussed and considered in *In re Petering* at 301 F.2d 676 at CCPA 1962; and *In re Schauman*, 572 F.2d 312, CCPA 1978. Apotex's reliance on these cases is misplaced.

The law has established that a claim to a species anticipates a genus, but a claim to a genus doesn't necessarily anticipate a species. *Eli Lilly*, and I cite here *Eli Lilly v. Barr Labs* at 251 F.3d 955 at 971, from the Fed. Cir. 2001. The '909 patent explicitly discloses one salt form of amlodipine as the preferred salt: the amlodipine maleate. The patent discloses other potential salt forms; indeed, it suggests at least a dozen. But the besylate salt is not included in the list. The '909 patent surely covers the besylate salt, but the Court finds as a matter of law that it does not disclose it.

A person of ordinary skill in the art looks in vain at the '909 patent to find anything other than amlodipine maleate to be the preferred product. The Court finds there is nothing in the '909 patent, let alone clear and convincing evidence, to show that it anticipates the '303 patent.

Defendants argue that the genus of pharmaceutically acceptable salts is small, thus a claim to the genus anticipates this finite species. They cite to the Berge article which was known at the time of the '909 patent, but the Berge article identifies more than 50 anions and lists the frequency of their use. Benzyl sulphonate is mentioned and noted to have been used .25 percent of the time. This is a mere one time in 400. It is scarcely to be suggested that this is a directive arrow pointed to by the '909 patent.

Apotex's argument is ultimately a linguistic and syllogistic argument. It goes as follows: First the '909 patent claims, quote, a pharmaceutical composition comprising an anti-ischaemic or anti-hypertensive amount of a compound according to claim 1, and a pharmaceutically acceptable diluent or carrier, that's JTX 40, and a pharmacologically accepted anion. Therefore, the '909 patent anticipates amlodipine besylate. The argument proves too much. There are, according to Berge, over 50 anions, which have historically been accepted by the FDA. That science will ultimately produce at least one more, and

probably many more, which will ultimately be accepted by the FDA, is a virtual certainty. If Apotex's argument is accepted, the '909 patent will anticipate products which have not yet been developed, but which may be later accepted at some later time by the FDA. This is not clear and convincing. Their anticipation arguments fail because the '909 patent discloses the genus and several specific salts, it does not disclose the benzene sulphonate, a species of the '909 genus. The patent is not anticipated.

I also refer to the fact that there is an allusion to the fact that the -- I should also note, that the evidence indicated the only prior uses of a besylate salt, for pharmaceutical purposes, was in a tranquilizer, and a veterinarian product, each of which is entirely unrelated to the product in question here. It does not appear that it has ever been used in any fashion for anything relating, ah, to a hypertensive or angina protecting preparation. There was a reference also, however, to the fact that in 1992 -- 1982 -- there was an experiment in which a sulphonate was used and obtained a salt. I recognize, however, that this was an experiment conducted by one Burges, referred to in Exhibit 21, but the product involved was methane sulphonate, and this scarcely, once again, directs a particular, ah, person, and I will focus further in a moment on the person, to produce a besylate salt. I note that the actual exhibit said that they "managed to form." Managing to form does not suggest anything along the line that this is pharmaceutically acceptable and will ultimately be a pharmaceutically acceptable process, or contain the necessary attributes.

I now focus on the fact that Apotex has advanced an estoppel argument. In doing so, they seize on typed words which Pfizer has submitted to the Patent Office and to the U.S. Court of Appeals for the Federal Circuit. In certain statements to that office and the Circuit, Pfizer stated that the '909 patent covers amlodipine besylate, for purposes of extending the '909 patent and in an action of infringement -- or for infringement of that patent. It is now Apotex's

argument that these statements are antithetical to Pfizer's claim that the '303 patent is for something new and shows somehow its acquiescence in Apotex's claim that the '909 patent anticipates and makes obvious the '303 patent. Remarkably, the Court notes that Harris Pitlick, Apotex's patent law expert, neither talked about nor did he offer any opinion on this theory. This is probably for the best, because as I've indicated, unlike, ah -- this is probably for the best, because unlike a truly hygroscopic salt, this theory does not hold water. The Court cannot gainsay the possibility that Apotex feels it does not need expertise on the subject, but the Court finds the argument weak in the extreme.

The Court is well satisfied that Pfizer's declarations are not at all inconsistent with its position in this case. Pfizer acknowledges that the '909 patent covers amlodipine besylate, but argues, and in this Court's view, argues persuasively, that the besylate salt of amlodipine is not disclosed by the '909 patent. This is the precise thesis set out in *In re Benno*, at 768 F.2d 1340 at 1346, Fed. Cir. 1985. This distinction is critical and not considered by Apotex, as the Court has now properly analyzed whether the '909 patent anticipates the '303.

Obviousness.

An invention cannot be patented if, in light of the prior art, the invention is obvious to one having ordinary skill in the art to which the patent pertains. I reference 35 U.S.C. Section 103(a). Here, the Court is called upon to define the person having reasonable skill in the art.

The Court finds that a person having ordinary skill in the art would have a bachelor's degree in pharmaceutical science or analytical chemistry, and some experience in drugs and drug preparation. For these purposes, the Court also assumes the person having ordinary skill in the art would also have the knowledge of organic chemistry. The Court rejects the suggestion offered by Apotex's expert, Dr. Cima, that a

person having ordinary skill would also possess an understanding of materia science and hydrolytic chemistry. This addition is rejected because it calls for expertise by hindsight. Pfizer and the world now know that amlodipine maleate could not be used to produce a stable commercial product. And we now know this is because of amlodipine maleate's exposure to water that when it is exposed to water, it undergoes a hydrolytic reaction, under which the product breaks down by the mechanism of the Michael Addition reaction, with resulting, ah, unsuitable, ah, byproducts. But all of this was unknown at the time of the '909 patent, when the future of amlodipine maleate was bright. Ultimately, the problem was hydrolytic, but it is only known and now made clear by hindsight. The requirement of hydrolytic chemistry is not a part of one skilled in the art at the time of the grant of the '909 patent. Finally on this point, I do note that under such a strict standard, the inventors themselves would not have possessed the ordinary skill to produce or understand their own art. But even were I to accept it, I do not find that that would lead a person to the obvious conclusions.

To show that the '303 patent is obvious, the defendant must show: One, the prior art suggests to those of ordinary skill in the art that they should make the claimed composition; and two, the prior art suggests a reasonable expectation of success. Here I cite *In re Vaeck*, 947 F.2d 488 at 493, Fed. Cir. 1991. The '303 patent's file wrapper shows that the examiner originally rejected the claimed invention because of obviousness. Under these circumstances, of course, the Court must accept that the defendant has made a prima facie showing on this question.

But this prima facie showing can be rebutted if the patentee can show that the invention has unexpectedly superior outcomes over the prior art. This requires a showing that the claimed invention is an improvement over the prior art, and the improvement was unexpected. I reference *In re Soni* at 54 F.3d 746 at 751, Fed. Cir. 1995; and *In re May* at 574 F.2d 1082 at 1094 and 5, CCPA 10 -- or 1978.

In this regard, Apotex claims again that the universe of pharmaceutically acceptable acid addition salts is small enough to render the use of one or another of them obvious. In doing so, they rely upon the Berge article to show that benzene sulphonate was a known FDA-approved salt -- or anion.

Though a known anion, it remains imperative to note that it reveals that benzene sulphonate, as noted before, was used in only .25 percent of the occurrences prior to the time of 1974. The patent examiner cannot have been aware of the Berge article as it was specifically noted and cited in the '303 patent itself. As such, the Court could not possibly find by clear and convincing evidence that the article and its teachings could not have been considered by the patent when ultimately determining whether the '303 patent was obvious, and in the examiner's determination that it was ultimately not obvious. The Berge article's listing of salt does not render the patent obvious.

The Berge article, however, is particularly enlightening on an additional point. As noted above and accepted by each of the experts who testified, quote: There is no reliable way of predicting the influence of a particular salt species on the behavior of a parent compound, close quote. That is from Berge on page 1. In essence, the formulation of a pharmaceutical salt is a trial and error process, with no guarantee, let alone an expectation of its success.

As to whether the besylate salt is an actual improvement over the maleate, the Court recognizes that while not superior to the maleate salt in every category, the besylate salt clearly and unexpectedly illustrates a superior combination of properties when compared to what was suggested as the preferred preparation, the maleate salt in the '909 patent. In addition to the evidence supplied by the exhibits in the patent, the Court notes the objective consideration that Pfizer would not have changed from the

maleate, into which it had invested both time and research dollars, to seek out a very strange and rare besylate salt, absent an extremely good reason. I find that the besylate salt was superior to the art.

And turning to inequitable conduct, the defendant argues that the '303 patent is unenforceable, because plaintiff Pfizer engaged in inequitable conduct before the Patent Office, in violation of its duty of candor, and its obligations of truth set forth at 37 C.F.R. Section 1.56.

Again, one seeking to invalidate a patent must prove this proposition by clear and convincing evidence. I cite for this proposition, and once again there are many cases setting it forth, *Allied Colloids v. American Cyanamid* at 64 F.3d 1570, 1578, Fed. Cir. 1995. Here a defendant is required to show both failure to disclose information material to patentability or intentional misrepresentation of a material fact and intent to deceive the Patent Office. Citing *Kingsdown v. Hollister* at 863 F.2d 867 at 872, Fed. Cir. 1988. Quoting here: After finding threshold levels of materiality and intent, the trial court must balance the two and determine in its discretion whether inequitable conduct has occurred, closing the quote. That's *Amgen v. Chugai* at 927 F.2d 1200 at 1215, Fed. Cir. 1991.

The defendant has identified several statements in the patent they argue are material misrepresentations, many of which have been referred to, and the Court resets its findings as previously set forth in this opinion's prior recitation. Apotex alleges the solubility of the besylate salt is fraudulently identified in the patent to be 4.6, while Pfizer documents show it to be 3.5 milliliters per, or milligrams per milliliter. The patent claims a thousand tablets were tested for processability, while Pfizer documents show varying numbers up to 150. And the patent's ordinal method of ranking stability is somehow fraudulent upon the Patent Office because it does not reveal that the differences between the besylate, tosylate, and mesylate are minor.

The Court, at the outset, records its findings that these are simply not material concerns. But even assuming that they were, the Court finds that while defendant has shown minor discrepancies between known research and the terms of the patent, the defendant has not shown any of the statements in the patent to be false. As previously noted, amlodipine besylate solid -- solubility is certainly above the 1.0 milligram per milliliter level which is the sought-after solubility. As for stability, the besylate maintains its integrity and is far better than the maleate, which suffers, as I've indicated, the Michael Addition reaction, which is part of the relevant prior art.

The Court finds that Apotex has failed to show anything approaching clear and convincing evidence touching the second element, intent to defraud. There is precious little evidence at all which might be claimed to show an intent to deceive on behalf of Pfizer. The missing notebooks, while troublesome, do not show an intent to deceive. While it is clear Pfizer was eager to extend the patent life of its amlodipine compound, such a desire does not rise to the level of fraudulent intent.

The proof in this Court's -- in this patent's worth is in the pudding. The besylate salt works, and it has been incredibly successful. No matter how valuable the discovery of amlodipine, it is useless, useless to the point of nearly being rejected for pharmacological use, until the discovery, and the Court finds it to be an exceptional discovery, the besylate salt which finally produced a reliable delivery system.

Amlodipine besylate is an invention in its own right, unanticipated, not obvious, and patented in good faith. The '303 patent is valid, enforceable, and would be infringed unless the defendants are restrained from producing their proposed product prior to the expiration of the '303 patent term. The Court finds as a matter of law that the defendants

have committed an act of infringement in filing an Abbreviated New Drug Application seeking to produce amlodipine besylate prior to that date. They will be enjoined from further proceedings in that regard. And that will be the order of the Court. I thank you.

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No. 06-1582

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IN THE

Supreme Court of the United States

PFIZER, INC.,

Petitioner,

v.

APOTEX, INC. (F/K/A TORPHARM, INC.),

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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BRIEF IN OPPOSITION

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PARTIES TO THE PROCEEDINGS

All parties to the proceeding are identified in the caption.

CORPORATE DISCLOSURE STATEMENT

Apotex Pharmaceutical Holdings, Inc. is the parent of Apotex, Inc. There are no publicly held companies that own 10% or more of the corporation's stock.

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BRIEF IN OPPOSITION

STATEMENT

Petitioner Pfizer, Inc. filed suit against respondent Apotex, Inc., alleging that Apotex's application for approval to market a generic version of Pfizer's amlodipine besylate drug product, which Pfizer markets under the trademark Norvasc® for treating hypertension and angina, infringed U.S. Patent No. 4,879,303 ("the '303 patent"). Pet. App. 1a. The '303 patent was Pfizer's second patent covering its popular Norvasc® heart medication. Pfizer held market exclusivity for Norvasc® for many years based on U.S. Patent No. 4,572,909 ("the '909 patent"), issued on February 25, 1982, that also covered Norvasc®. Pet. App. 3a-4a.[1] Apotex denied infringement

[1] In fact, Pfizer applied for and received a 1,252 day patent term extension for the '909 patent specifically based on the time it took the FDA to

and contested the validity of the patent on grounds of obviousness. Pet. App. 2a. After a bench trial, the district court entered judgment for Pfizer and enjoined Apotex from marketing its generic until September 25, 2007. Pet. App. 2a. Although the '303 patent expired on March 25, 2007, Pfizer received an additional six month period of marketing exclusivity during which time the FDA would forego granting final approval to generic competitors as a result of its agreement to conduct tests to determine the efficacy of amlodipine besylate in children, if Pfizer met certain statutory requirements. Pet. 5-6, 16.

On March 22, 2007, the court of appeals reversed, concluding that the '303 patent was invalid for obviousness. Pet. App. 38a. As the court noted, "a claimed invention is unpatentable if the differences between it and prior art 'are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.'" Pet. App. 18a (quoting 35 U.S.C. § 103(a)). In this case, the active ingredient identified in the '909 patent, amlodipine, is the same as the active ingredient in the '303 patent. The '909 patent also claimed all pharmaceutically acceptable acid salts of amlodipine, of which besylate is one. Pet. App. 4a-5a; 18a. The '909 patent noted that the preferred salt form was the maleate. Pet. App. 4a-5a. However, Pfizer had difficulty producing amlodipine maleate in commercial tablet forms. Pet. App. 4a-5a. Standard laboratory practices eventually determined that besylate salt would be preferable for marketing a tablet, and although its initial efforts to obtain a patent for amlodipine besylate were rejected by the Patent Office as obvious, eventually Pfizer obtained the '303 patent. Pet. App. 6a-9a, 29a-30a. The court of appeals found that there was clear and convincing evidence that "one skilled in

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approve Pfizer's Norvasc® (amlodipine besylate) product, which is expressly claimed in the '303 patent as well. *See Pfizer, Inc. v. Dr. Reddy's Labs.*, 359 F.3d 1361, 1364 (Fed. Cir. 2004).

the art would have been motivated to combine the teachings of the '909 patent, Berge [a leading scholarly article in the field], and other prior art, to produce the besylate salt of amlodipine." Pet. App. 23a. The evidence also showed that there was a reasonable expectation of success when using besylate as an addition salt. Pet. App. 23a-26a. After rejecting Pfizer's claim that the evidence showed no more than it would have been obvious to try amlodipine besylate (Pet. App. 26a-32a), and after finding that Pfizer failed to prove any secondary considerations sufficient to overcome the strong showing of obviousness (Pet. App. 32a-37a), the court of appeals held the '303 patent invalid and unenforceable. Pet. App. 38a.

On May 21, the court of appeals denied Pfizer's petition for rehearing and rehearing en banc and granted Apotex's motion for immediate issuance of the mandate. Pet. App. 39a-40a. On May 30, Pfizer filed a petition for certiorari along with motions to recall and stay the mandate of the court of appeals and to expedite consideration of the petition for certiorari. On June 6, Justice Stevens denied the motion to recall and stay the mandate, and on June 11, the court denied the motion to expedite. On June 14, Pfizer filed a letter with the FDA seeking to have the '303 patent delisted from the FDA's Approved Drug Products List with Therapeutic Evaluations Equivalents on the ground that the '303 patent could no longer be asserted against any entity marketing a generic equivalent of amlodipine besylate. Supp. Br. 1.

ARGUMENT

Pfizer does not seek plenary review. Instead, it seeks vacatur of the judgment of the court of appeals and a remand directing that court to reconsider this case in light of this Court's decision in *KSR Int'l Corp. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). In fact, the court of appeals has already considered *KSR* as it ruled on Pfizer's petition for rehearing; a remand for reconsideration would therefore be pointless.

Moreover, there is no tension between the decision below and *KSR*; if anything, this Court's holding in *KSR* suggests that the Federal Circuit has unduly circumscribed the defense of obviousness, and any error on that score would inure to Pfizer's benefit. Moreover, in this case and in its other recent decisions, the Federal Circuit has adopted an approach to obviousness that anticipated the holding in *KSR*. Just as the Court recently denied a petition for certiorari in another case from the Federal Circuit taking the same approach as the decision below, the Court should deny certiorari here.

Pfizer also argues that if this Court does not rule on its petition for certiorari until after the period of pediatric exclusivity expires on September 25, 2007, it should vacate the judgment of the court of appeals as moot. In fact, it is far from clear that this case will be moot after September 25; it is only Pfizer's tactical decision to abstain from seeking the remedies that may be available at that point that supports its claim for mootness. A party is not, however, entitled to vacatur of an unfavorable judgment on grounds of mootness merely as a consequence of its litigation tactics.

1. Pfizer does not claim that this case merits plenary review. Indeed, Pfizer's petition presents only two questions – the first requests summarily vacating the judgment of the court of appeals and remanding for further consideration in light of *KSR*, and the second seeks vacatur of the judgment of the court of appeals as moot if the petition is not granted prior to September 25, 2007. *See* Pet. i. Under its rules, this Court will consider only the questions set out in a petition for certiorari. *See* Sup. Ct. R. 14.1(a). Thus, while Pfizer claims that the decision below is out of step with *KSR* and will call into question the validity of many patents (Pet. 8, 14-15), it apparently recognizes that this assertion does not support plenary review. The Federal Circuit will have many opportunities to assess the consistency of the holding below with *KSR*. Moreover, if, in the future, this Court perceives that the

Federal Circuit is unwilling or unable to hew to the holding in *KSR*, it will have ample opportunity to provide correction.

2. Instead of plenary review, Pfizer seeks summary vacatur of the judgment of the court of appeals and a remand directing that court to reconsider the case in light of its *KSR* decision. *See* Pet. 9. The court of appeals, however, has already considered *KSR* as it ruled on Pfizer's petition for rehearing and rehearing en banc; and not a single member of that court thought that anything in *KSR* warranted any alteration in its judgment in this case.

Nearly a month before the court of appeals denied its petition for rehearing, Pfizer brought *KSR* to the attention of that court of appeals in support of its petition for rehearing, as Pfizer acknowledges. See Pet. 6. Apotex's motion to issue the mandate, filed while the petition for rehearing remained pending, also brought this Court's decision in *KSR* to the attention of the court of appeals, and Pfizer again addressed *KSR* in its response to that motion. See Opposition to Motion to Stay and Recall Mandate Exhs. A & B (No. 06A1131). Even aside from the parties' filings in the court of appeals, it would be absurd to believe that the judges of the Federal Circuit would not have bothered to read a decision of this Court dealing with subject matter of intense concern to that specialized court.[2] In any event, the court of appeals denied Pfizer's petition for rehearing and issued its mandate immediately, and of the twelve judges who acted on the petition for rehearing en banc, only three voted to grant it, despite Pfizer's claim that KSR supported its position. See Pet. App.

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[2] Indeed, the Federal Court had already evinced its awareness that this Court had granted plenary review in *KSR* even before this Court's opinion came down. *See DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Co.*, 464 F.3d 1356, 1367 n.3 (Fed. Cir. 2006) ("Indeed, the United States Supreme Court recently granted certiorari in a case involving this court's application of the suggestion test."), *cert. denied*, 75 U.S.L.W. 3661 (U.S. June 11, 2007) (No. 06-1207).

39a-40a. Perhaps of even greater importance, none of the three judges who voted to grant rehearing accused the panel's holding of reflecting any inconsistency with *KSR*. *KSR* appeared in one of the dissenting opinions only to support the proposition that "[c]hemical and pharmaceutical compounds often can be found to be prima facie obvious, as they are based on prior work that could reasonably suggest them." Pet. App. 49a (Lourie, J., dissenting).

In short, it is plain that the court of appeals was fully aware of *KSR* as it denied Pfizer's petition for rehearing. A remand for reconsideration would impose a pointless burden on the court of appeals.

3. The court of appeals was quite right to conclude that there was no tension between the holding below and this Court's decision in *KSR*. Although Pfizer claims that the court of appeals erred by applying a version of its teaching, motivation, suggestion test ("TSM") in invalidating the asserted claims of Pfizer's patent, *see* Pet.12-14, that claim will not bear scrutiny.

At the outset, Pfizer does not argue that under *KSR*, it is impermissible to assess these factors in undertaking an obviousness inquiry. To the contrary, *KSR* is quite clear that the TSM test is consistent with the leading case on the defense of obviousness, *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), so long as the TSM inquiry is not used to unduly circumscribe the defense:

> Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility. In the years since the Court of Customs and Patent Appeals set forth the essence of the TSM test, the Court of Appeals no doubt has applied the test in accord with these principles in many cases. There is no necessary inconsistency between the idea under-

> lying the TSM test and the *Graham* analysis. But when a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs.

KSR, 127 S.Ct. at 1741. In *KSR*, the Court simply rejected the Federal Circuit's use of an overly rigid application of the TSM test that left the obviousness defense unduly circumscribed.

> The flaws in the analysis of the Court of Appeals relate for the most part to the court's narrow conception of the obviousness inquiry reflected in its application of the TSM test. In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under *§ 103*. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

Id. at 1742.

Thus, *KSR* broadened the defense of obviousness in comparison to the test that the Federal Circuit had employed in that case. For that reason, Pfizer's reliance on *KSR* is more than a little anomalous. In *KSR*, this Court held that a sensor for a position-adjustable vehicle pedal assembly was invalid on grounds of obviousness, overturning the approach taken by the Federal Circuit, which had improperly limited that defense. *See* 127 S. Ct. at 1739-46. There is no reason to believe that a second look at *KSR* would convince the court of appeals to uphold Pfizer's patent when it had already invalidated that patent on grounds of obviousness. If anything, it is the dissenting opinions below, on which Pfizer bases its request for this petition that appear out of step with *KSR*. *Compare KSR*, 127 S. Ct. at 1742 ("The same constricted

analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'") with Pet. App. 41a (Newman, dissenting) ("The panel's application of the obvious-to-try standard is in direct conflict with precedent . . . . '[W]e have consistently held that 'obvious to try' is not to be equated with obviousness.'" (quoting *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990)).

Indeed, rather than reflecting inconsistency with *KSR*, the decision below anticipated its holding by adopting a flexible conception of obviousness:

> [A] suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." In other words, it is irrelevant that none of the anions specifically listed in the '909 patent have a cyclic structure, because the motivation to make amlodipine besylate here is gleaned not only from the prior art as a whole rather than the '909 patent alone, but also from the nature of the problems encountered with the amlodipine maleate tablet formulations sought to be solved by the inventors of the '303 patent.

Pet. App. 19a-20a (citations omitted) (quoting *DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006), *cert. denied*, 75 U.S.L.W. 3661 (U.S. June 11, 2007) (No. 06-1207)).

Pfizer also notes that the Court in *KSR* "reaffirmed the notion that where combinations yield unexpected results, the unexpected nature of the results cuts against a finding of obviousness." Pet. at 13. But in the decision below, the Federal Circuit expressly recognized that unexpected results may overcome a showing of prima facie obviousness. Pet.

App. 33a ("Evidence of unexpected results can be used to rebut a prima facie case of obviousness."). It then devoted several pages of its decision to explaining why the results touted in Pfizer's patent were not unexpected at all in view of the prior art before concluding: "Pfizer has simply failed to prove that the results are unexpected." Pet. App. 36a.

Accordingly, there is no tension between the decision below and *KSR*. To the contrary, in *KSR*, this Court characterized the case on which the court of appeals primarily relied below, *DyStar* (Pet. App. 18a, 20a, 27a, 31a), as "elaborat[ing] a broader conception of the TSM test than was applied in the instant matter," and added that the approach taken in *DyStar* was "not now before us . . . ." 127 S. Ct. at 1743. Thus, there is no inconsistency between *DyStar* and *KSR*, as this Court has already recognized. Just weeks ago, the Court denied a petition for certiorari in *DyStar*, rather than vacating and remanding for reconsideration in light of the intervening decision in *KSR*. *See DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Co.*, 75 U.S.L.W. 3661 (U.S. June 11, 2007) (No. 06-1207). There is no more reason to vacate and remand in this case.

Thus, nothing in *KSR* warrants vacatur of the judgment of the court of appeals and a remand for reconsideration. The decision below was based on *DyStar* and not the approach that this Court rejected in *KSR*. It is presumably for that reason that even the dissenting judges below saw nothing in *KSR* that supported their view on the validity of the '303 patent.

4. Pfizer argues that after the expiration of the statutory period of pediatric exclusivity on September 25, 2007, the judgment of the court of appeals should be vacated as moot because Pfizer's rights flowing from the patent will have expired. *See* Pet. 16-19. It is, however, far from clear that this case will be moot after September 25.

Under the statutory pediatric exclusivity provision, a patented drug already gains an additional six months of exclusivity for a patent holder that undertakes pediatric testing of the drug at the FDA's request. *See* 21 U.S.C. § 355a(c)(2). Thus, "[u]nder the statute . . . the patent holder is eligible to receive a six-month period of market exclusivity for the drug beyond the patent expiration date." *Mylan Laboratories, Inc. v. Thompson*, 389 F.3d 1272, 1276 (D.C. Cir. 2004). In this case, however, were Pfizer to eventually sustain the '303 patent on the merits, it would have been deprived of its rights to six months of pediatric exclusivity as a result of an erroneous judicial decision invalidating that patent. Although Pfizer now disclaims any ability to obtain a decision on the merits after September 25, it is far from clear that the statute offers Pfizer no remedy for such a deprivation of statutory rights, should it ultimately prevail in this action.

In *Astrazenica AB v. Impax Laboratories, Inc.*, No. 00 CIV. 7597(BSJ), 01 CIV. 2998(BSJ), M-21-81 (BSJ), MDL 1291, 2007 WL 1612053 (S.D.N.Y. May 25, 2007), for example, the court held that the expiration of the original rights under a patent coupled with the FDA's approval of generic equivalents for marketing did not moot an infringement action brought during the period of pediatric exclusivity, reasoning: "The Court agrees that the six-month period of pediatric exclusivity does not extend the term of the patents, but it does grant the patent holder a period of market exclusivity, which this Court has the power to enforce." *Id.* at *7. As the decision in *Astrazenica* suggests, it is far from clear that Pfizer will have no remedy after September 25 if it ultimately prevails in this action and establishes that the judgment of the court of appeals wrongfully cut short its period of statutory exclusivity. If it were to uphold the patent on remand from this Court, perhaps the court of appeals would then conclude that the district court has the power to enjoin Apotex and perhaps even others from further marketing of its generic equivalent for an additional period of time until Pfizer

has received a full six-months of exclusivity. Or, perhaps the court will conclude that Pfizer is entitled to seek damages from Apotex.

To be sure, nothing in the applicable statute expressly grants a patentee a right of action against competitors if it believes it has been wrongly deprived of its right to six months of statutory exclusivity. Still, an implied right of action could be derived from the statute. Traditionally, this Court has looked to four factors in endeavoring to determine whether an individual right of action can be implied from a statute – whether the plaintiff is a member of a class for whose special benefit the statute was enacted; whether there is any indication of a legislative intent to grant or deny such a remedy; whether it is consistent with the underlying purposes of the statute to imply a remedy; and whether the subject matter at issue is traditionally governed by state law. *E.g.*, *Cort v. Ash*, 422 U.S. 66, 78 (1975). The Court has more recently stressed that the statute must manifest an intent to create enforceable private rights for a private right of action to be implied. *See, e.g.*, *Gonzaga University v. Doe*, 536 U.S. 273, 283-84 (2002). It is certainly far from clear how this inquiry should be resolved in this case. Perhaps the statute should be read as merely a directive to the FDA; indeed, it is clear that Congress intended many aspects of the Food and Drug Act to be policed exclusively by the FDA. *See, e.g.*, *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 348-52 (2001). Nevertheless, in light of the manifest statutory intent to provide patentees with assurances of exclusivity should they agree to the FDA's requests for pediatric studies, coupled with Congress's understandable failure to anticipate a situation in which an erroneous judicial decision cuts short the period of exclusivity, the requisite intent to create a private remedy could well be present.

In any event, even if no private right of action to enforce the statutory right of exclusivity can be implied, perhaps the

FDA would itself take action to grant Pfizer an additional period of exclusivity should it ultimately prevail in this case. In *Mylan Laboratories*, for example, the FDA revoked its order approving the marketing of a generic drug following a district court's decision upholding the patent on that drug and enforcing the patentee's right of pediatric exclusivity. *See* 389 F.3d at 1277-78. The court upheld this action as a reasonable effort to administer an ambiguous statute. *See id.* at 1281-84. As the decision in *Mylan* suggests, the FDA takes the right to pediatric exclusivity seriously, and its efforts to protect those rights will receive deference on judicial review. Were Pfizer to ultimately prevail in this case, the FDA might itself choose to revoke the right of generic competitors to market their drugs for a period of time in order to grant Pfizer a full six months of exclusivity.

To be sure, the answer to the question whether Pfizer might have some remedy after September 25 should the judgment of court of appeals be vacated is unclear; we have no confidence in the outcome of that inquiry, and we certainly intend to concede nothing through the instant submission. What is clear, however, is that the party asserting mootness has the burden of establishing that the parties no longer have any meaningful stake in the outcome of the litigation. *See, e.g., Cardinal Chemical Co. v. Morton International, Inc.*, 508 U.S. 83, 98 (1993). It is equally clear that a party cannot obtain vacatur of an unfavorable judgment as moot because of its voluntary litigating decisions; indeed, the Court has written that "[t]he principal condition to which we have looked is whether the party seeking relief from the judgment below caused the mootness by voluntary action." *U.S. Bancorp Mortgage Co. v. Bonner Mall Partnership*, 513 U.S. 18, 24 (1994). Thus, Pfizer's tactical decision not to press any right it might have to seek either a judicial or administrative remedy after

September 25 surely cannot entitle it to vacatur of the judgment below.[3]

What is more, vacatur is an equitable remedy, and "[i]t is petitioner's burden, as the party seeking relief from the status quo of the appellate judgment, to demonstrate . . . equitable entitlement to the extraordinary remedy of vacatur." *U.S. Bancorp.*, 513 U.S. at 26. Pfizer's case on the equities, however, is particularly weak. Not only has it already enjoyed the full period of patent protection for the '303 patent as well as a portion of the period of pediatric exclusivity, but its petition makes no effort to consider the potential for a judicial or administrative remedy after September 25. Surely it is the burden of those who seek equitable relief to make a proper and detailed showing that they have no other remedy available. *See, e.g., FCC v. Radiophone, Inc.*, 516 U.S. 1301, 1301 (1995) (Stevens, J., in chambers) ("I am persuaded, however, that allowing the national auction to go forward will not defeat the power of the Court of Appeals to grant appropriate relief in the event that respondent . . . prevails on the merits."). That showing is entirely absent in the petition. Perhaps it will come in the reply brief, when we will have no opportunity to respond, but that is doubtless too late for equity to countenance.

Indeed, the equitable case for vacatur is especially weak since the petition is without substance. As we explain above, there is no basis here for either plenary review or a remand for reconsideration. The right to press a petition for certiorari that Pfizer claims it is losing due to the passage of time is accordingly worthless; there is nothing remotely certworthy about this case. Pfizer should not be able to obtain vacatur of

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[3] For this same reason, Pfizer's decision to voluntarily delist the '303 patent cannot entitle it to vacatur on grounds of mootness. Indeed, Pfizer acknowledges that "the delisting letter does not moot this case." Supp. Br. 2.

an unfavorable precedent merely because events may have overtaken an otherwise worthless petition for certiorari. Just as Justice Stevens found nothing about this case that warranted the equitable relief of a recall and stay of the mandate, nothing in the petition supports the equitable relief of vacatur.

CONCLUSION

The petition for writ of certiorari should be denied.

Respectfully submitted,

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IN THE

Supreme Court of the United States

PFIZER INC.,

Petitioner,

v.

APOTEX, INC. (formerly known as TorPharm, Inc.),

Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

REPLY FOR PETITIONER

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REPLY FOR PETITIONER

Three judges, dissenting from the denial of rehearing *en banc* in this case, decried the grave consequences the panel decision will have for pharmaceutical patents. Pet. App. 41a-51a. Yet the judgment embodied in that panel decision was reached without benefit of this Court's later-decided opinion in *KSR International Corp. v. Teleflex Inc.*, 550 U.S. ___, 127 S. Ct. 1727 (2007). Respondent nonetheless claims that the Federal Circuit must have "read [that] decision" (Opp. at 5), and "was fully aware of *KSR*" (*id.* at 6), in the course of silently rejecting Pfizer's *en banc* petition. But as this Court outlined in *Lords Landing Village Condominium Council of Unit Owners v. Continental Insurance Co.*, 520 U.S. 893 (1997), even where a lower court makes an "ambiguous statement" about the effect of an intervening decision—which surely demonstrates that the lower court has "read" and "was fully aware of" the new decision—that is not enough to avoid the need for a GVR order. *See* pp. 2-4, below.

Respondent is also wrong to say that "Pfizer does not claim that this case merits plenary review." (Opp. at 4) Pfizer does so claim, and the case does merit plenary review. *See* Pet. at 8 ("The importance of the issues in this case . . . would surely qualify this case for plenary review."); *see also* Br. *Amicus Curiae* of Wash. Legal Found. at 2 ("*Amicus* Br."). But Pfizer seeks GVR not merely because of the Federal Circuit's inexplicable silence in the wake of the milestone *KSR* decision, but also because Pfizer's remaining rights under the '303 patent evaporate on September 25, 2007. *See* Pet. at 16; Pet'r's Supp. Br. at 1-2. GVR is the only meaningful opportunity Pfizer has to secure any review of this decision at this point, lest the case become moot by the passage of time.

If the case does become moot, then, as Pfizer showed (Pet. at 16-19), the Federal Circuit's judgment should be vacated under *United States v. Munsingwear, Inc.*, 340 U.S. 36

(1950), and *U.S. Bancorp Mortgage Co. v. Bonner Mall Partnership*, 513 U.S. 18 (1994). If that happens, Respondent would retain a case-specific victory on mootness grounds. But apparently that is not enough for Respondent, which now argues *against* a mootness victory by suggesting that Pfizer's pediatric exclusivity period may not actually end on September 25, 2007, and that Pfizer may be entitled to relief, including monetary damages, beyond that date. Respondent is wrong to suggest those theories, which are blocked by statute and by this Court's own precedents, even though Pfizer would otherwise welcome that possibility. *See* pp. 5-8, below.

As we showed in the Petition, and show again below, vacatur of the Federal Circuit's decision—whether because of the Federal Circuit's failure to give proper consideration to *KSR* or on mootness grounds—is the appropriate course here.

* * * *

1. Despite the Federal Circuit's telling silence on the issue, Respondent claims that "the court of appeals ... has already considered *KSR*" in this case, because it must have "read" (Opp. at 5) and been "fully aware of *KSR*" (*id.* at 6), and that "there is no tension between the holding below and [] *KSR*." *Id.* Those claims cannot withstand scrutiny.

Obviously, the March 22, 2007 panel decision could not have considered *KSR*, which this Court issued on April 30, 2007. *See* Pet. at 6. And suppositions that the judges of the Federal Circuit were "aware of" or had "read" *KSR* while the *en banc* petition was still pending are not enough to dispel the need for a GVR order. In *Lords Landing Village Condominium Council of Unit Owners v. Continental Insurance Co.*, 520 U.S. 893 (1997), resolution of the case turned on a state-law question. After the federal court of appeals decided the state-law question and issued its mandate, the state supreme court announced a new decision calling the circuit court's resolution of the state-law issue

into doubt. There, as here, the parties made the appeals court aware of the decision. Indeed, in *Lords Landing*, the court of appeals issued a written order whose sole purpose was to discuss whether the new decision "required a different disposition of this case." *Id.* at 898 (Rehnquist, C.J., dissenting) (describing lower court's order). So the court of appeals there had unquestionably "read" and was "aware of" the intervening decision.

This Court nonetheless entered a GVR order: The intervening decision provided "reason to question the correctness of the Court of Appeals' decision," and "the Court of Appeals' ambiguous statement that petitioner's request was 'without merit' does not establish that it actually considered and rejected petitioner's . . . argument" based on the intervening decision. *Id.* at 896-97. Here, the Federal Circuit stood entirely silent on the effect of *KSR*. And that silence, even more than the Fourth Circuit's "ambiguous statement" in *Lords Landing*, "does not establish that it actually considered and rejected petitioner's . . . argument" regarding *KSR*. *Id.* at 897. *See also Thomas v. Am. Home Prods., Inc.*, 519 U.S. 913, 915 (1996) (Scalia, J., concurring).

Nor can Respondent sidestep the need for a GVR order by the oversimplified claim (Opp. at 7) that *KSR* "broadened the defense of obviousness" in comparison to the Federal Circuit's earlier tests. For one, *KSR* itself declared that question to be "a matter for the Court of Appeals to consider in its future cases." 550 U.S. at ___, 127 S. Ct. at 1743. For another, the Federal Circuit's first post-*KSR* obviousness decision, *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157 (Fed. Cir. 2007), did not apply *any version* of the controversial teaching-suggestion-motivation test that served as the basis for the Federal Circuit's decision here. That leaves substantial doubts about the continued validity of the panel decision's reasoning in this case. *Compare id.* at 1161-62 *with* Pet. App. 18a-23a. Finally, even if one considers *KSR* to have "broadened" the obviousness defense,

that is not necessarily true across the board, as Pfizer showed in the Petition (at 12-14): Much of this Court's *KSR* opinion focused on when combined elements work together in an "unexpected and fruitful manner." 550 U.S. at ___, 127 S. Ct. at 1740 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)). Such "surprising results" were not present in the simple mechanical device at issue in *KSR*, but they are often—as the district court here found (Pet. App. 10a-11a)—present in chemical and pharmaceutical inventions. *Amicus* WLF sets forth a number of the district court's findings in this respect (*Amicus* Br. at 4-5); the Federal Circuit should apply the rulings of *KSR* to these facts expressly, not (as Respondent claims) *sub silentio*.

The Court's similarly silent denial of certiorari in *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 75 U.S.L.W. 3661 (U.S. June 11, 2007) (No. 06-1207), likewise does not mean, as Respondent claims (Opp. at 9), that the "this Court has already recognized" that *DyStar* (and by extension this case, which relied on *DyStar*) is consistent with *KSR*. It is "well-settled" that "denial of certiorari imparts no implication or inference concerning the Court's view of the merits," *Hughes Tool Co. v. Trans World Airlines, Inc.*, 409 U.S. 363, 365 n.1 (1973), and it bears further note that DyStar's petition neither sought GVR nor presented the question at the heart of this case; rather, it presented three other diffuse questions—one about the Seventh Amendment, one factbound question about the objective indicia of nonobviousness in that case, and a third regarding a supposed "new corroboration requirement for all testimony in patent cases." Pet. for Cert. at i, *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, No. 06-1207, 2007 WL 683959 (Mar. 5, 2007). Particularly in that light, no inferences can or should be drawn from the denial of certiorari in *DyStar*.

KSR made important changes to the law of obviousness. The Federal Circuit should have at least attempted to square a decision with such broad ramifications and severe

consequences with *KSR*. That is precisely what the GVR remedy is designed to accomplish.

2. In the alternative, Pfizer has urged the Court—if it is unable to review this case prior to September 25, 2007—to grant the petition and vacate the decision below under *Munsingwear* and *Bonner Mall*, because the expiration of Pfizer's pediatric exclusivity on that date will end the last legal right Pfizer has associated with the '303 patent. *See* Pet. at 16-19.

Although this alternative remedy would leave Respondent with a victory in this particular dispute (because Respondent is now competing in the market with a generic version of Pfizer's Norvasc®, and would stay in the market unaffected), that is seemingly not enough. Respondent has now suggested (without "intend[ing] to concede" anything, *see* Opp. at 12) that this case may not become moot on September 25, 2007, when Pfizer's pediatric exclusivity ends, because, *inter alia*, there are theories under which Pfizer might sue Respondent. Respondent's newly crafted theories are unavailing, and do not stand in the way of vacatur for mootness.

There is no realistic possibility that Pfizer will be able to obtain monetary or other relief under Respondent's theories. The pediatric-exclusivity period that Pfizer has lost by this decision does not extend the patent term. *See* 21 U.S.C. § 355a(c)(2)(B) ("the period during which an application may not be approved . . . shall be extended by a period of six months *after the date the patent expires* (including any patent extensions)") (emphasis added). And, as this Court has held, the Food, Drug and Cosmetic Act (FDCA) "leaves no doubt" that private litigants may not sue for noncompliance. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 n.4 (2001). So it is not feasible that a controversy will continue to exist in this case after September 25, 2007.

Indeed, the fact that Respondent is now positing a number of theories under which it might be liable for hundreds of millions of dollars in damages is a strong indication that Respondent does not seriously believe any of them has merit. In fact, Respondent's own descriptions of these theories of recovery acknowledge just how dubious they are, with its choice of words emphasizing the shaky foundation on which they are constructed. *See* Opp. at 9 ("far from clear"), 10 ("far from clear" and "perhaps" both repeated twice), 11 ("perhaps" repeated three times; "[t]o be sure, nothing in the applicable statute expressly grants a patentee a right of action against competitors . . . [s]till, an implied right of action could be derived from the statute"), 12 ("the FDA might itself choose to revoke the right of generic competitors to market their drugs for a period of time in order to grant Pfizer a full six months of exclusivity"). Respondent itself summarizes the nature of its suggested remedies in these words: "To be sure, . . . whether Pfizer might have some remedy after September 25 . . . is unclear; we have no confidence in the outcome of that inquiry." Opp. at 12.

But all of Respondent's theorizing about other claims that Pfizer "might," "perhaps" bring in the future can be swept to the side, because they are far different than the infringement claim that Pfizer brought in this case. And "[t]he mootness of petitioner['s] claim at the present stage of the proceedings must be assessed on the basis of what that claim *is*." *Grupo Mexicano de Desarrollo S.A. v. Alliance Bond Fund, Inc.*, 527 U.S. 308, 315 n.2 (1999) (emphasis in original).*

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* Even if Respondent's newly hypothesized claims *were* feasible ones, which they are not, and *were* present in this case, which they are not, vacatur and remand would still be the appropriate course. *See, e.g., Diffenderfer v. Cent. Baptist Church of Miami, Fla., Inc.*, 404 U.S. 412, 415 (1972) (remanding case, which had become moot by the Florida legislature's repeal of the challenged statute and replacement with a different one, because plaintiff might wish to amend its complaint "to

Notwithstanding Respondent's contrary contentions (Opp. at 13-14), the equities here only favor vacatur. Pfizer has attempted to protect its remaining rights with vigor and promptness. The decision below is of questionable merit: No court has even *attempted* to square that decision with *KSR*, and it rests on shaky legal foundations as underscored by not one, not two, but three separate district courts having found that the patented invention here was not obvious. *See* Pet. at 1 n. *, 18 (noting the *Mylan* and *Synthon* cases, both of which have now been reversed by the Federal Circuit based on the preclusive authority of the panel decision below). If left standing without the opportunity for further review, it will "call[] into question countless pharmaceutical patents, which in turn could have a profoundly negative effect on investments into the design and development of new life-saving pharmaceuticals." Pet. App. 51a (Rader, J., dissenting from the denial of rehearing *en banc*).

Against all of these equitable factors stand only (i) Respondent's unsupported (and demonstrably incorrect) suggestion that Pfizer's is a "worthless ... petition for certiorari" (Opp. at 13), which is, at minimum, offensive to the three dissenting judges in the Court of Appeals, and (ii) Respondent's bizarre claim that because Justice Stevens denied (without comment) Pfizer's application to recall the mandate, that act somehow simultaneously disentitled Pfizer from the equitable relief of vacatur. *Id.* at 14.

Respondent has failed to identify any way in which it or the public would be harmed either by a GVR order or by an order vacating the decision below under *Munsingwear*. The harm to Pfizer, and to the public, by contrast, is manifest. Pet. at 14-15; *Amicus* Br. at 1-2. It would be wrong to saddle

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demonstrate that the repealed statute retains some continuing force or to attack the newly enacted legislation").

the pharmaceutical industry, and by extension the public that relies on those pharmaceuticals, with an unworkable and incorrect rule of law on obviousness merely because the rights associated with the '303 patent expired before this Court had an opportunity to undertake review.

CONCLUSION

For these reasons, and those set forth in the Petition, the petition should be granted, and the judgment of the Court of Appeals vacated.

Respectfully submitted,

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July 11, 2007

(2)

No. 06-1582

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IN THE

Supreme Court of the United States

PFIZER INC.,

Petitioner,

v.

APOTEX, INC. (formerly known as TorPharm, Inc.),

Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

SUPPLEMENTAL BRIEF IN SUPPORT OF PETITION FOR A WRIT OF CERTIORARI

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In its petition for certiorari (filed May 30, 2007), Pfizer has sought review of the Federal Circuit's judgment declaring U.S. Patent No. 4,879,303 ("the '303 patent") invalid on obviousness grounds. The '303 patent covers amlodipine besylate, the active ingredient in Norvasc®, which is the world's largest selling brand-name drug for treating hypertension.

In addition to filing the petition for certiorari, Pfizer also asked the Court to recall and stay the Federal Circuit's mandate, and to expedite consideration of the petition. On June 6, 2007, Justice Stevens denied the application to recall and stay the mandate, and on June 11, 2007, the Court denied the motion to expedite.

On June 14, 2007, in response to these decisions, Pfizer filed a letter with the Food and Drug Administration seeking to have the '303 patent delisted from the FDA's Approved Drug Products List with Therapeutic Equivalence Evaluations (commonly referred to as the "Orange Book"). Pfizer was compelled to submit this letter because, in view of the Federal Circuit's ruling, and this Court's recent decisions on the above-referenced motions, the '303 patent could not, under the present state of facts, "reasonably be asserted" against any company manufacturing a generic version of amlodipine besylate. *See* 21 U.S.C. § 355(b)(1)(G). A copy of that letter is reproduced in the Appendix to this Supplemental Brief (at 1-2).

The purpose of this Supplemental Brief is to apprise the Court of this delisting letter, and to explain that the letter does not interfere with the Court's consideration of Pfizer's petition for certiorari. In particular, the letter does not moot further consideration of that petition.

As the petition explains, the '303 patent expired on March 25, 2007. *See* Pet. at 6. Under the Better Pharmaceuticals for Children Act, however, Pfizer was entitled to an

additional six-month period of exclusivity, the so-called pediatric exclusivity period,* during which the FDA would not approve Abbreviated New Drug Applications (ANDAs) for generic equivalents to Norvasc. *Id.* To be sure, now that Pfizer has requested the delisting of its patent, the '303 patent does not—under the present posture of this case—block FDA approval of competing manufacturers' ANDAs for generic amlodipine besylate. If the Court decides Pfizer's petition before September 25, 2007 (the end of the statutory six-month exclusivity period) and vacates the decision below as Pfizer has requested, then there would be a reasonable basis for asserting the '303 patent, and Pfizer can seek to have the '303 patent relisted. Such a relisting would reinstate the pediatric exclusivity period, thereby returning to Pfizer at least some benefit from the statutory exclusivity to which it was entitled. Accordingly, the delisting letter does not moot this case.

If, on the other hand, the Court does not rule on the petition until after September 25, 2007, then the case *will* become moot as a result of the expiration of the pediatric exclusivity period itself. *See* Pet. at 16-19. At that point, the '303 patent would have no more exclusionary force, as both the patent and its associated pediatric exclusivity period would have expired—meaning that there would no longer be a live controversy. In that circumstance, as described more fully in the petition, *see id.*, under *United States v. Munsingwear, Inc.*, 340 U.S. 36 (1950) and *U.S. Bancorp Mortgage Co. v. Bonner Mall Partnership*, 513 U.S. 18 (1994), the Court should vacate all of the decisions below, as

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* The "pediatric exclusivity period" is so named because it provides for an additional six months of market exclusivity as an incentive for new drug manufacturers to conduct pediatric studies requested by the Food and Drug Administration. *See* 21 U.S.C. § 355a(b). The market exclusivity extends to all uses of the drug, whether in children or adults.

the case would have become moot due to events beyond Pfizer's control.

Respectfully submitted,

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APPENDIX

June 14, 2007

VIA FEDERAL EXPRESS
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PATENT INFORMATION

Re: NDAs 19-787 and 21-540

Dear Ms. Holovac:

Pfizer is hereby notifying FDA that Patent No. 4,879,303 no longer meets the legal criteria for listing in the "Orange Book." Thus, please remove (or "de-list") the '303 patent from the Orange Book listings for NDAs 19-787 (Norvasc®) and 21-540 (Caduet®).

On March 22, 2007, the Court of Appeals for the Federal Circuit (CAFC) held that the claims of the '303 patent covering the besylate salt of amlodipine were invalid for obviousness. The CAFC denied Pfizer's motion for rehearing *en banc* and issued its mandate on May 21. Pfizer immediately sought certiorari from the U.S. Supreme Court, and moved (i) to have the mandate recalled and stayed, and (ii) to have the consideration of its petition expedited. On

June 6, the Supreme Court denied Pfizer's motion to recall the CAFC's mandate and stay the case while Pfizer's petition for certiorari was pending. Further, on June 11 the Supreme Court denied Pfizer's motion to expedite consideration of its petition for writ of certiorari.

Pfizer will continue to seek the Supreme Court's review of the Federal Circuit's decision. Nonetheless, in light of the Federal Circuit's mandate and the Supreme Court's decisions with respect to Pfizer's motions, the '303 patent no longer meets the patent listing criteria set forth in 21 USC 355(b)(1), because the patent now cannot "reasonably be asserted" against an unlicensed manufacturer of amlodipine besylate. Thus, Pfizer is compelled to request that the '303 patent be removed from the Orange Book.

Thank you very much for your attention to this matter.

Very truly yours,

/s/ Bruce A. Pokras

Bruce A. Pokras

cc: U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
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JUN 2 9 2007

(3)

No. 06-1582

IN THE

Supreme Court of the United States

PFIZER, INC.,
Petitioner,

v.

APOTEX, INC.
(formerly known as TORPHARM, INC.),
Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

MOTION FOR LEAVE TO FILE BRIEF AND BRIEF OF WASHINGTON LEGAL FOUNDATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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MOTION OF WASHINGTON LEGAL FOUNDATION FOR LEAVE TO FILE BRIEF AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

Pursuant to Rule 37.2 of the Rules of this Court, the Washington Legal Foundation (WLF) respectfully moves for leave to file the attached brief as *amicus curiae* in support of Petitioner. Counsel for Petitioner has consented to the filing of this brief. Counsel for Respondent declined to provide consent, thereby necessitating the filing of this motion.

WLF is a non-profit public interest law and policy center with supporters in all 50 states. WLF devotes a substantial portion of its resources to defending and promoting free enterprise, individual rights, and a limited and accountable government. In particular, WLF has appeared before this Court and other federal courts in numerous cases raising important issues regarding the scope and validity of pharmaceutical patents. *See, e.g., Ferring B.V. v. Barr Laboratories*, 437 F.3d 1181 (Fed. Cir.) (patent invalidated based on inequitable conduct), *cert. denied*, 127 S. Ct. 515 (2006); *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005) (patent invalidated based on inherent anticipation), *cert. denied*, 126 S. Ct. 2887 (2006); *Pfizer, Inc. v. Dr. Reddy's Laboratories, Ltd.* 359 F.3d 1361 (Fed. Cir. 2004) (scope of patent protection); *Allergan, Inc. v. Alcon Laboratories, Inc.*, 324 F.3d 1322 (Fed. Cir.) (scope of causes of action under 35 U.S.C. § 271(e)(2)), *cert. denied*, 540 U.S. 1048 (2003); *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001) (Hatch-Waxman Act procedures for resolving drug patent disputes), *cert. denied*, 537 U.S. 941 (2002).

WLF fully supports Petitioner's request that the Court grant review in this case. WLF writes separately in order to emphasize its particular concern over the practical impact of the Federal Circuit's decision. The issue of patent obviousness

is one of significant concern to the business community. In recognition of that concern, this Court very recently granted review in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), and provided helpful guidance regarding when an invention should be deemed obvious and thus unpatentable. Rather that taking that guidance to heart, the Federal Circuit denied panel rehearing and rehearing *en banc* in this case – thereby keeping in place a pre-*KSR* decision that is at considerable tension with *KSR*. WLF is concerned that the Federal Circuit itself may draw the same erroneous conclusion from the denial of rehearing in this case as does Respondent: that the initial panel decision must be consistent with *KSR* because the panel was aware of *KSR* for a full month prior to acting on the rehearing petition yet chose not to reconsider its views. To the contrary, there is *no* evidence to suggest that the panel gave any serious consideration to the effects of *KSR* on this case. Had any such consideration been given, it is difficult to believe that the panel could have overlooked the numerous inconsistencies between its opinion and *KSR*. WLF is concerned that unless this Court, at a minimum, remands the case and compels the Federal Circuit to take another careful look at it, the Federal Circuit will accept the panel decision as an accurate translation of *KSR*'s guidance regarding when a patent should be deemed obvious.

WLF is also concerned that by issuing a decision that throws into question the validity of a wide range of pharmaceutical patents, the Federal Circuit will undermine confidence in the nation's patent system as an effective means of protecting intellectual property rights, and thus reduce incentives for companies to invest in new, life-saving therapies.

WLF is filing this brief because of its interest in promoting the welfare of the health care industry and the public at large; it has no direct interest, financial or other, in the outcome of this lawsuit. Because of its lack of direct

economic interests, WLF believes that it can assist the Court by providing a perspective that is distinct from that of any party.

For the foregoing reasons, the Washington Legal Foundation respectfully requests that it be allowed to participate in this case by filing the attached brief.

Respectfully submitted,

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QUESTIONS PRESENTED

Whether the Federal Circuit's failure to reconsider its judgment under the obviousness standard established by *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), merits granting the petition and vacating the judgment, given the tension between the *KSR* standard and the one adopted herein by the Federal Circuit, particularly in the unpredictable pharmaceutical arts?

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Miscellaneous:

P.J. Federico, *Commentary on the New Patent Act*,
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Giles S. Rich, *Principles of Patentability*,
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BRIEF OF WASHINGTON LEGAL FOUNDATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

INTERESTS OF *AMICUS CURIAE*

The interests of *amicus curiae* Washington Legal Foundation (WLF) are set forth in the motion accompanying this brief.[1]

STATEMENT OF THE CASE

This Court should grant *certiorari* because there are significant issues of public policy at stake. In the decision below, the Federal Circuit ignored evidence of unexpected results in an unpredictable technology, discounted the value of the invention in violation of 35 U.S.C § 101, and impermissibly focused on the manner in which the invention was made in violation of the clear language of 35 U.S.C. § 103(a). By so doing, the Federal Circuit's opinion will lead to decreased investment in research and development and increased litigation costs in the pharmaceutical industry.

In addition, the Federal Circuit's opinion contradicts this Court's recent decision in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), which issued while Pfizer's petition for rehearing *en banc* was pending. In *KSR*, the Court expressly stated that factors such as the predictability of the art and unexpected results are important considerations in determining whether an invention is obvious, particularly in a complex technological art, such as pharmaceuticals. Rather than taking the opportunity to conform to the standard of *KSR*,

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[1] Pursuant to Supreme Court Rule 37.6, WLF states that no counsel for a party authored this brief in whole or in part; and that no person or entity, other than WLF and its counsel, contributed monetarily to the preparation and submission of this brief.

the Federal Circuit denied Pfizer's *en banc* petition (over three dissenting opinions), causing continued uncertainty, especially in the area of pharmaceutical inventions. App. 39a-51a.

As stated by Judge Newman, dissenting from the Federal Circuit's decision not to rehear the case *en banc*, "[t]he panel decision changes the criteria as well as the analysis of patentability, with results of particular significance for their efforts on the conduct of R&D, the costs of drug development, and the balance between generic access to established products and the incentive to development of new products." App. 42a (Newman, J., dissenting). Similarly, Judge Lourie wrote that the Federal Circuit's "failure to recognize all such properties that may be relevant to the value of . . . a compound may doom the compound to being poured down the drain rather than becoming an important therapeutic." App. 49a (Lourie, J., dissenting). And Judge Rader explained that the "decision calls into question countless pharmaceutical patents, which in turn could have a profoundly negative effect on investments into the design and development of new life-saving pharmaceuticals." App. 51a (Rader, J., dissenting).

Accordingly, *amicus* WLF submits that this case would be a perfect vehicle to address the Court's holding in *KSR* and apply it in the context of the pharmaceuticals art. However, given the procedural posture of the case and the relevant expiration date of the patent at issue (as noted in Petitioner's brief), and the extraordinary importance of the decision to the pharmaceutical industry, *amicus* WLF requests that at the very least, this Court vacate the decision below and either remand for further proceedings in light of *KSR* or vacate the decision as moot in light of *United States v. Munsingwear, Inc.*, 340 U.S. 36 (1950), for the reasons set forth in Petitioner's Brief, at 16-19.

REASONS FOR GRANTING THE PETITION

I. *Review Is Warranted Because the Federal Circuit* Improperly Discounted Evidence of Unexpected Results in an Unpredictable Technology

KSR reaffirmed that when determining whether a patent claiming a combination of prior art elements was obvious "a court must ask whether the improvement is more than the *predictable use* of prior art elements according to their established functions." *KSR*, 127 S. Ct. at 1740 (emphasis added). The Court further confirmed the value of unexpected results in assessing the nonobviousness of an invention. Citing its prior opinion in *United States v. Adams*, 383 U.S. 39 (1966), the Court explained that "[w]hen Adams designed his battery, the prior art warned that risks were involved in using the types of electrodes he employed. The fact that *the elements worked together in an unexpected and fruitful manner* supported the conclusion that Adams's design was not obvious to those skilled in the art." *KSR*, 127 S. Ct. at 1740 (emphasis added).

The invention claimed in this case involves a distinct chemical compound – amlodipine besylate – which comprises two sub-elements chemically bound to each other: an active pharmaceutical component (amlodipine as a cation) and an acid addition salt anion (besylate a/k/a benzenesulfonate).[2] Unlike other salts in its class and those identified in the prior

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[2] In that sense, the subject matter of this patent is quite unlike the patent at issue in *KSR*, which involved a combination of pre-existing devices (a brake pedal and a sensor) tacked together in a new way. Amlodipine besylate is a distinct chemical compound, not a combination of things tacked together; it should not be viewed as a "combination" patent.

art, the besylate salt unexpectedly provided superior stability, solubility, and stickiness properties without the associated tradeoffs in bioavailability and efficacy. App. 5a-8a. The uncontested testimony and evidence show that these improvements were not predictable:

- "The district court . . . stated that the besylate salt of amlodipine was unexpectedly superior to the amlodipine salts of the prior art. . . . [I]t . . . 'clearly and unexpectedly illustrates a superior combination of properties' . . . ." App. 10-11a (citation omitted).

- "The district concluded that [a prior art article] does not direct the skilled artisan to create the besylate salt of amlodipine because [the article] discloses that besylate sulphonate was used only at a frequency of 0.25%, or 1 out every 400 drugs, prior to 1974." App. 10a.

- "Nor was there any evidence contradicting Pfizer's position that 'the superior properties at issue were not some abstract concept of "good" properties, but specific properties which solved both the sticking and instability problems of the prior art, while providing non-hygroscopicity and good solubility.'" App. 42a (Newman, J., dissenting) (citation omitted).

- "Trade-offs in salt properties are the rule, and one of skill must usually accept some undesirable properties to achieve other desirable ones. Amlodipine besylate [the claimed invention], unlike any other amlodipine salt, presented no trade-offs." *Id.*

- "[T]he besylate salt clearly and unexpectedly exhibited a superior combination of properties when compared to

what was suggested in the preferred preparation." App. 47a (Lourie, J., dissenting)(citation omitted).

- "As the testimony indicated, the properties of new pharmaceutical salt forms are entirely unpredictable." App. 50a (Rader, J., dissenting).

There was simply no basis for the Federal Circuit to ignore these unexpected results in such an unpredictable technology — particularly where there was no showing that any of the factual findings made by the district court were clearly erroneous. The Federal Circuit's decision to do so contradicts the Court's precedent in *KSR*, represents a profoundly bad public policy, and warrants review by the Court.

II. Review Is Warranted Because the Federal Circuit Completely Discounted the Value of the Invention in Violation of 35 U.S.C. § 101

The Federal Circuit avoided a review of the unexpected results by focusing only on the overall efficacy of the compound, holding "that the optimization of the acid addition salt for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation has no effect on the *therapeutic effectiveness* of the active ingredient . . ." App. 31a (emphasis added). As stated by Judge Rader (writing in dissent), "[t]he panel also mistakenly determined that the superior properties of the besylate did not overcome a prima facie case of obviousness because they showed no superior therapeutic value . . . ." App. 51a (Rader, J., dissenting).

With this opinion, the Federal Circuit has effectively deemed a critical field of pharmaceutical research unworthy of

patent protection. The evidence unambiguously established that the purpose of formulating amlodipine into a besylate salt was to solve problems unique to pharmaceutical development — to find a salt form that has superior stability, solubility, and "stickiness" *without* tradeoffs in bioavailability and efficacy. App. 5a-8a.

In drug development, such problems are far from trivial, and an acceptable solution is rarely predictable. The successful balancing of desirable product attributes such as drug shelf life, solubility, potency, toxicity, and efficacy is often critical to the ultimate success of a candidate drug, and medicinal chemists and formulation scientists commonly spend inordinate amounts of time, money, and effort on finding solutions to such problems.

The Federal Circuit's decision to ignore such important properties frustrates the goal of pharmaceutical research and does not represent a correct view of the law. "Therapeutic value, however, is just one property of a pharmaceutical. Other properties, such as solubility, stability, hygroscopicity, and processability, must also play a role in the analysis of advantages." App. 51a (Rader, J., dissenting). Indeed, Congress specifically authorized issuance of patents on any new and useful improvement of an existing inventions. 35 U.S.C. § 101 (2000). All that is required for patentability is a beneficial effect on some property or attribute of the basic invention that is not predictable.

This case involves a very narrowly claimed invention — a particular salt form of a single, known molecular species. The undisputed evidence in this case shows that the particular salt form claimed represents a non-obvious improvement because, in the as-yet unpredictable art of pharmaceutical formulations, the advantages of the patented invention

compared to the closest prior art salt forms could not have been reasonably predicted. If the benefits of the claimed invention at issue in the present case were indeed trivial, a competitor would have used one of the salts specifically disclosed in the prior art. As Judge Rich observed nearly half a century ago: "A monopoly on something nobody wants is pretty much . . . a nullity. That is one of the beauties of the patent system. The reward is measured automatically by the popularity of the contribution." Giles S. Rich, *Principles of Patentability*, 28 Geo. Wash. L. Rev., 393, 402 (1960).

The popularity of the present invention, and thus its value, has been endorsed in this case by the conduct of the accused infringer. In order to sell amlodipine, it was not necessary to copy the present improvement invention. Congress authorized two pathways for obtaining approval for follow-on drug products under sections 505(b)(2) and 505(j), respectively, of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 355(b)(2), 355(j) (2000). Section 505(b)(2) provides a mechanism for seeking approval to market a modified but nonetheless bioequivalent formulation, such as a different and unpatented salt form. *See Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361, 1364 (Fed. Cir. 2004). The infringer here, however, selected the 505(j) pathway for approval by making a literal copy of the patented salt form. Thus, the actual copying of the patented invention — in lieu of practicing any of a host of readily available, but unpatented, alternatives — demonstrates the error in the Federal Circuit's discounting of the importance of the invention.

As recognized by Judge Lourie (writing in dissent), "the panel improperly placed greater importance on the therapeutic value of a claimed compound over the value of its physical properties . . . . I read that conclusion as improperly requiring a compound to posses a specific type of improvement over the

prior art – in this case, improved therapeutic properties – to be patentable, negating other important properties, a conclusion that is not compelled by our case law and not sound." App. 47a-48a (Lourie, J., dissenting). Judge Lourie is correct and review by this Court is warranted to correct this clear error of law.

III. Review Is Warranted Because the Federal Circuit Erred in Ignoring the Express Provisions of 35 U.S.C. § 103(a)

Certiorari review is further warranted because the Federal Circuit erred in ignoring the express provisions of 35 U.S.C. § 103(a). If the decision is allowed to stand, it will adversely impact the direction and amount of pharmaceutical research.

The Federal Circuit looked at the process by which the unique properties of the besylate salt were discovered and concluded that because it was the result of "routine experimentation" it should not be patentable. App. 31a-32a; App. 48a (Lourie, J., dissenting). This, of course, is contrary to 35 U.S.C. § 103(a), which expressly states that "[p]atentability shall not be negatived by the manner in which the invention was made." App. 48a (Lourie, J., dissenting); App. 51a (Rader, J., dissenting). This provision was added to the Patent Act of 1952 to make clear that "it is immaterial whether it resulted from long toil and experimentation or from a flash of genius." P.J. Federico, *Commentary on the New Patent Act*, 75 J. Pat. & Trademark Off. Soc'y 161, 184 (1993). By emphasizing the manner in which the invention was made, the Federal Circuit failed to follow the legislative intent and important public policy goals underlying the Patent Act.

A critical element of pharmaceutical research and development involves systematic and persistent investigation using well-characterized techniques and principles. This research "is fundamental to scientific advance, and particularly for biological and medicinal products, where small change can produce large differences." App. 42a (Newman, J., dissenting). The Federal Circuit's decision is contrary to the legislative intent of § 103(a) and threatens the incentive to invest in pharmaceutical research.

IV. Review Is Warranted Because the Federal Circuit Erred When it Examined Obviousness from the Perspective of the Inventor

In *KSR*, the Court explained that "[t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art." *KSR*, 127 S. Ct. at 1742; *see also Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("Because patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art, information regarding the subjective motivations of inventors is not material."); *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("Inventors, as a class, . . . possess something . . . which sets them apart from the workers of *ordinary* skill, and one should not go about determining obviousness . . . by inquiring into what *patentees* . . . would have known or would likely have done, faced with the revelations of references."). Here, however, the Federal Circuit analyzed the obviousness issue by improperly focusing on the *inventor's own thought processes*: "Dr Wells' testimony reflects the fact that *he believed* that amlodipine besylate would solve the problems of amlodipine maleate." App. 36a (emphasis added); *see also* 24a, 28a, 37a. The Federal Circuit's rationale was tantamount

to *sub silentio* adoption of a "reasonable to the inventor" standard.

Not only is this standard inconsistent with controlling precedent, but such a standard would obviate a large percentage of goal-oriented pharmaceutical research. Laboratory notebooks often clearly state the objective of an experiment and the hoped-for results before an experiment is performed. Testing the predictive value of laboratory research is central to the scientific-method and is not an accurate indication of the required reasonable expectation of ultimate success. The Federal Circuit's rationale provides a powerful incentive for scientists not to articulate the results they hoped to achieve in their experiments because of the risk of invalidating any patent later sought for their invention. Furthermore, a pharmaceutical company would worry that the justification to continue or begin a project could later be used as evidence that the result was expected and therefore obvious. The Federal Circuit's decision in this regard contradicts the well-established precedent of this Court, represents poor public policy, and warrants the grant of *certiorari*.

CONCLUSION

For all the above reasons, *amicus* Washington Legal Foundation respectfully requests that the Court grant the petition for a writ of *certiorari*. At the very least, the Court should vacate the decision of the Federal Circuit and remand for further proceedings in light of this Court's decision in *KSR*.

Respectfully submitted,

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